101ST CONGRESS
1st Session

COMMITTEE PRINT

S. PRT.
101-000

Pharmacotherapy: A Strategy for the 1990's

A STAFF REPORT

Prepared for the Use of the

COMMITTEE ON THE JUDICIARY
UNITED STATES SENATE

ONE HUNDRED FIRST CONGRESS

FIRST SESSION

DECEMBER 13, 1989

U.S. GOVERNMENT PRINTING OFFICE
24-612 O WASHINGTON : 1989

5522-4

COMMITTEE ON THE JUDICIARY

JOSEPH R. BIDEN, JR., Delaware, *Chairman*

EDWARD M. KENNEDY, Massachusetts
HOWARD M. METZENBAUM, Ohio
DENNIS DeCONCINI, Arizona
PATRICK J. LEAHY, Vermont
HOWELL HEFLIN, Alabama
PAUL SIMON, Illinois
HERBERT KOHL, Wisconsin

STROM THURMOND, South Carolina
ORRIN G. HATCH, Utah
ALAN K. SIMPSON, Wyoming
CHARLES E. GRASSLEY, Iowa
ARLEN SPECTER, Pennsylvania
GORDON J. HUMPHREY, New Hampshire

RONALD A. KLAIN, *Chief Counsel*
DIANA HUFFMAN, *Staff Director*
JEFFREY J. PECK, *General Counsel*
TERRY L. WOOTEN, *Minority Chief Counsel and Staff Director*

FOREWORD

We often describe drug abuse as an "epidemic" in our country. The description is perhaps more fitting then most people realize. For like other epidemics, the drug abuse epidemic has—at its core—a complex set of medical causes that must be addressed.

Thus far, our national policy with respect to drug abuse has been to focus on social policies that are needed to educate potential victims of the dangers of this "disease," and to prevent its further transmission by punishing those who spread it for profit. Fortunately, these social answers to drug epidemic are finally beginning to be seriously addressed.

Unfortunately—and perhaps surprisingly—we have done very little as a country to address the *medical* dimension of this illness.

> *Put simply: If drug abuse is an epidemic, are we doing enough to find a medical "cure" for this disease? As this Staff Report indicates, the answer to this question is "no."*

As this Report shows, there are promising new medicines that appear to lessen addicts' cravings for cocaine and heroin, as well as to reduce their enjoyment of those drugs. Other medicines can ease the pain an addict suffers when he attempts to break his habit.

The eight promising new treatments identified by this Report should be among our highest medical research priorities as a nation. The fact is, however, that they are not.

The blame for this failure lies in many quarters. Researchers in academia and the public sector have failed to do their part in pioneering new treatment medicines. Private industry has shown too little interest in pursuing new medicines once discovered. Congress has failed to adopt some long-proposed measures that could speed approval of promising new treatments.

And perhaps most disappointing of all, the President's first National Drug Control Strategy Report failed to identify accelerated pharmacotherapy research as a priority. Indeed, the Report recommended an increase of just $20 million for research in this field—providing an *annual* budget which just barely equals the research dollars spent every *day* on the Star Wars program.

This Report builds, in my view, a persuasive case for a new National Strategy to hasten the development of anti-drug abuse medicines. The goals it offers are realistic, yet ambitious; the five-point plan it recommends for reaching these goals reflects a consensus of many of the nation's leading experts.

I agree with the Report's conclusion that we must vastly increase our spending on research in this area, reform our regulatory scheme to speed up the development and delivery of these treatments, target resarch on the most important areas, and hold the bureacuracy accountable with tough, but reachable goals.

The need to accelerate our efforts in the field of pharmacotherapy is clear:

- As it stands, a medicine that will block addicts' enjoyment of cocaine—thereby reducing their demand for it—is barely visible on the horizon. As a result, it probably will not be available until the next century. If we take the steps outlined in this Report, however, we may have such a drug in use in this country by 1997.
- A medicine that will be effective in simultaneously blocking the effects of cocaine and heroin (an increasingly popular combination) is even further out of sight. If we take the steps urged here, such a treatment should be available for use by 1999.

The benefits for our country of such a strategy are manifold. If we reduce the number of men and women addicted to drugs, we reduce the number of crimes committed in our streets, the number of babies born with deformed bodies and brains, and the number of children approached by drug-dependent pushers. Each dollar we spend on the approach outlined here can save us 10 or 20 times as much in the years ahead.

The question isn't "Can we afford a National Pharmacotherapy Strategy?," but rather, "Can we afford to continue without one?"

Given the state of current medical research identified by this Report, I believe that effective pharmaceutical treatment for drug abuse is no pipe dream, but I also see that—absent decisive action taken today—the progress of our researchers in developing drug treatments will continue to lag behind the progress of the drug dealers in developing new substances for abuse.

We must act boldly, and we must act now.

* * * * * * *

In closing, I want to thank the many experts who were good enough to give their time to brief me and my staff. Those experts include: Dr. Karst Besteman, Alcohol & Drug Problems Association of North America; Dr. Lee Cummings, National Institute of Drug Abuse; Dr. Walter Faggett, Substance Abuse Services; Dr. James Halikas, University of Minnesota; Dr. Thomas Kosten, Yale University School of Medicine; Dr. Gerald Mossinghoff, Pharmaceutical Manufacturers Association; Dr. Robert Newman, Beth Israel Medical Center; Dr. Charles O'Brien, Addiction Research Center; Dr. Carl Peck, Food & Drug Administration; Dr. Melvin Sabshin, American Psychiatric Association; Drs. Charles Schuster, Marvin Snyder, and Frank Vocci, National Institute of Drug Abuse; and Dr. Stanley Yancovitz, Beth Israel Medical Center. The listing of these experts is not meant to imply their endorsement of this Report.

I also want to thank the Judiciary Committee staff members who contributed to the preparation of this Report. They include John Bentivoglio, Paul Bland, Ann Howard, Scott Green, Ron Klain,

Chris Putala, and Ross Mansbach. Special credit must go to Paul Bland, Chris PUtala, and particularly Ross Mansbach, who devoted countless hours to developing the data and conclusions found here.

When the Senate reconvenes next year, I intend to introduce legislation to implement the recommendations of this Report. I urge my colleagues to review this Report carefully, and join me in supporting the measures recommended by it.

JOSEPH R. BIDEN, Jr,
Chairman.

December 13, 1989

EXECUTIVE SUMMARY

America's drug problem is reduced each and every time a drug user quits his or her habit. Any idea, any program that might help drug users conquer their addiction must be explored. This attitude is not motivated by mere sympathy for drug addicts; it pays off for all of us in dollars and cents. Fewer drug addicts means fewer crimes—fewer muggings, burglaries and murders—as well as fewer hospital admissions, drug-addicted babies and neglected children.

Unfortunately, America has not adequately explored one of the most hopeful treatment options—pharmacotherapy for illicit drug use.

Pharmacotherapy employs medicines to treat the disease of drug addiction. Recent medical advances have increased the possibility of developing medications to treat drug addiction. These advances include a heightened understanding of the physiological and psychological characteristics of drug addiction and a greater base of neuroscientific research.

Some pharmacotherapeutic medications seek to reduce the craving for illicit drugs. Others curb the pain of withdrawal from drugs such as heroin or cocaine. Still others seem to block the effects of illicit drugs. All such medications will augment other drug treatment methods, thereby increasing the efficiency of existing programs.

Of course, drug addiction often results from other personal problems. Pharmacotherapy will not address these problems and must be accompanied by psychiatric and other forms of counseling. Still, pharmacotherapy—as a treatment for drug users not helped by traditional methods, as a means of extending our limited drug treatment budget, as a way of easing the trouble addicts have in giving up their habits—holds substantial promise for reducing the health and crime crisis that drug abuse is causing America.

Unfortunately, a range of effective pharmacotherapies for our two most troublesome drug problems—cocaine and heroin—are not yet available. Only two medications, methadone and naltrexone, are currently approved by the Food and Drug Administration for drug abuse treatment. More and better therapeutics are needed for the treatment of opiate addictions. Several drugs are now being studied for their efficacy in treating cocaine addictions. Therapies must also be developed to treat victims of poly-drug (i.e., two or more drugs) abuse. Finally, we must anticipate the need for other therapeutics to treat the as yet unknown drug addictions of the 1990's.

The U.S. Food and Drug Administration's approval process has unnecessarily restricted the development of pharmacotherapy. The average time for clinical testing and FDA approval exceeds 9 years. Painstaking documentation of the safety and efficacy of treatments ensures that the cures are not worse than the disease. However, as

exceptional measures have been taken to hasten the development of AIDS treatments, the FDA's standards should be changed in the face of another life threatening disease: drug addiction.

The pharmaceutical industry has not emphasized the development of medications for illicit drug abuse. According to a recent Pharmaceutical Manufacturers Association survey of its member companies, 13 respondents did report ongoing pharmacotherapeutic research programs.[1] This survey indicates that private industry does devote a portion of its resources to drug treatment research. But that portion is not nearly large enough.

Private industry has not aggressively developed pharmacotherapeutics for a variety of reasons: They include a small customer base and the difficulties of distributing treatment medications to that population.

It is clear that, absent vastly increased government involvement, pharmacotherapeutics will not be developed at a rapid pace.

Some of the problems slowing the development of pharmacotherapies have technological solutions. For example, long-lasting therapeutics save patients the trouble of daily trips to a clinic and limit the risk that the medications will be diverted to illicit markets. More significantly, the greatest obstacle to immediate use of a cocaine blocking agent, for example, is that no such medication exists. The answers to these problems must be found in research labs.

There are some problems, however, that will only yield to careful, effective management by government regulators. These problems, too, need to be addressed.

The President's National Drug Strategy does not include a comprehensive strategy for the development of pharmacotherapies. The need for such a strategy is clear—researchers are learning more every day, but turning their ideas into medications will require a comprehensive plan. The strategy must draw on the nation's university and research institutes, private industry, and government agencies.

This report proposes a national strategy to accelerate the research, development and production of pharmacotherapeutics. This strategy sets 10 clear goals; tough, but attainable targets to deliver pharmacotherapies before the start of the 21st century. Of these 10, two stand out as the most important to the country:

- Bringing a pharmacotherapy for cocaine dependency to the marketplace by 1996, and
- Providing pharmacotherapeutic treatment on demand for both heroin and cocaine dependencies by 2000.

To realize these goals, the report proposes five initiatives:

First, launch a renewed Medications Development Program with funding of $1 billion over the next decade, accountable to a set of realistic but ambitious goals. The program should be a consortium effort modeled after the National Cancer Institute. Second, modify the Orphan Drug Act by extending the act's protection to include pharmacotherapies and enforcing the act's protection of new uses of old drugs.

---

[1] From a letter of Dec. 1, 1989, written by the Pharmaceutical Manufacturers Association to the U.S. Senate Judiciary Committee.

Third, hasten the delivery of safe drug treatments by employing the innovative procedures used by the Food and Drug Administration for AIDS treatments to medicines for drug abuse. Also, we should reform Food and Drug Administration procedures to forego "mechanism of action" requirements, and institute a "rolling IND" procedure.

Fourth, designate a few areas of top priority research, including the use of pharmacotherapeutic agents on pregnant women and their fetuses, treatments for the "new" drugs of the 1990's, and the interaction between heroin and cocaine addictions.

And, fifth, order the Surgeon General to produce a report on pharmacotherapy, similar to Dr. Koop's AIDS report.

CONTENTS

	Page
Foreword by Chairman Biden	iii
Executive summary	vii
I. An introduction to pharmacotherapy and several issues surrounding it	1
The objectives of pharmacotherapy	1
The definition of addiction	1
An explanation for drug use	2
A theory for drug treatment	2
Reasons for pharmacotherapy	3
Arguments against expanding pharmacotherapy research	4
The FDA approval process	6
Reasons for the pharmaceutical industry's apprehension of pharmacotherapy	7
II. Pharmacotherapy for narcotics abuse	8
Theories of narcotics addiction reversal	8
Background	8
Theories	9
Methadone	9
History	9
Pharmacology	10
Dosage and administration	10
Adverse effects	11
Effectiveness	11
Controversies	11
LAAM	15
History	15
Pharmacology	16
Dosage and administration	16
Adverse effects	16
Effectiveness	17
Controversies	17
Naloxone	18
History	18
Pharmacology	18
Dosage and administration	19
Adverse effects	19
Effectiveness	19
Controversies	20
Naltrexone	20
History	20
Pharmacology	20
Dosage and administration	21
Adverse effects	21
Effectiveness	21
Controversies	21
III. Pharmacotherapy for cocaine abuse	22
Theories of cocaine addiction reversal	22
Background	22
Theories	23
Imipramine	24
History	24
Pharmacology	24
Adverse effects	25
Effectiveness	25

Page

III. Pharmacotherapy for cocaine abuse—Continued
Diltiazem 25
History 25
Pharmacology 25
Adverse effects 26
Effectiveness 26
Carbamazepine 26
History 26
Pharmacology 26
Adverse effects 27
Effectiveness 27
IV. Poly-Drug Pharmacotherapies 27
Buprenorphine 27
History 27
Pharmacology 28
Adverse effects 28
Effectiveness 28
Issues 29
V. Recommendations 30
Goals for a pharmacotherapy strategy 30
The strategy in outline 31
1. Launch a renewed "Medications Development Program" 32
2. Modify the Orphan Drug Act 34
A. Extend the Orphan Drug Act's protection to include pharmacotheraputics 34
B. Stiffen the Orphan Drug Act's enforcement mechanisms 34
3. Hasten the use of new drug treatments 35
A. Institute "Treatment Investigational New Drugs" 35
B. Institute "Parallel Track Trials" 35
C. Forego "Mechanism of Action" requirement for previously approved pharmacotherapeutics 36
D. Legislate a "Rolling IND" Concept for Pharmacotherapeutics .. 36
4. Designate three new topics "Top Priority" at the MDP 37
A. The effects of pharmacotherapeutics on pregnant women and their fetuses 37
B. Treatments for "new" drugs of the 1990s 37
C. The proposed inter-action between heroin and cocaine pharmacologic mechanisms 37
5. Produce a Surgeon General's report on pharmacotherapy 37

PHARMACOTHERAPY: A STRATEGY FOR THE 1990's

I. An Introduction to Pharmacotherapy and Several Issues Surrounding It

Over the past 25 years, social perceptions of drug use have evolved dramatically. Perceptions have also changed in the scientific community. In particular, scientists' definition of addiction and their understanding of substance abuse have broadened to yield a new method of combatting drug use. This method is pharmacotherapy.

This report will:

- Analyze the reasons for promoting pharmacotherapy,
- Discuss eight promising drug treatments; and
- Recommend certain measures for enhancing pharmacotherapeutic research, development, and distribution.

THE OBJECTIVES OF PHARMACOTHERAPY

Pioneered in the mid-1960's, pharmacotherapy for illicit drug use employs chemicals to treat the symptoms and disease of drug addiction. For the purposes of this report, the term "pharmacotherapy" will refer to this treatment method, and the term "pharmacotherapeutics" will refer to the medications used to help recovering addicts.

The National Institute on Drug Abuse (NIDA) lists five objectives for pharmacotherapeutic development. The list reveals the medications' comprehensive nature; they can act effectively at every stage of drug addiction. The objectives are:

(1) To block the effects of abused drugs,
(2) To reduce the craving for abused drugs,
(3) To moderate and/or eliminate withdrawal symptoms,
(4) To block and/or reverse toxic effects, and
(5) To prevent, under certain conditions, initial drug abuse.[1]

THE DEFINITION OF ADDICTION

Researchers are developing pharmacotherapeutics mainly for two drugs of abuse: narcotics (such as heroin) and cocaine.

In the 1960's and 1970's, narcotics presented the greatest illicit drug threat to America. Accordingly, scientists first began to develop drug treatments for narcotics addiction. The predominant definition of addiction during this time included the concepts of tolerance and physical dependence, which are the hallmarks of chronic narcotics abuse.

Under this early definition, cocaine might not be considered an addictive substance. Because many scientists, in fact, did not be-

[1] *NIDA Notes*, Vol. 4. No. 1, Winter 1988/1989, p. 3.

lieve it addictive, little was done to treat those who abused the drug. Conventional wisdom held that its abusers could stop at will, and certainly without the aid of treatment drugs.

The development of pharmachotherapeutics for cocaine abuse had to wait until the mid-1980's. By then, the size of America's cocaine problem had ballooned and the scientific community's definition of addiction had evolved to include cocaine abuse.

In 1985, one scientific researcher expressed the changing beliefs of his colleagues when he expanded the definition of addiction to include behavorial aspects. He wrote that addiction constitutes "the loss of control over the intake of a drug that that leads to its compulsive use despite harmful effects in some area of the person's functioning." [2] This definition includes the indications of cocaine abuse.

The National Institute on Drug Abuse does not yet have a standard definition of addiction for research purposes.[3] Still, it is clear that today's popular and scientific definitions of addiction include both physical and mental facets of dependency.

This changing understanding of addiction has spurred interest in pharmacotherapy.

AN EXPLANATION FOR DRUG USE

New explanations for drug use have also promoted interest in pharmacotherapy.

A current hypothesis presents insight into the basic contention that, despite the broad dangers involved, a person uses drugs because they are momentarily enjoyable. The hypothesis on which scientists have concentrated for the last decade involves "brain reward circuitry." [4] As psychologists explain, people seek drugs to activate the brain's reward system, "a neural network responsible for the subjective experience of pleasure." [5]

In the case of cocaine, users experience pleasure when they stimulate certain neurons in their central nervous systems. Similarly, in the case of narcotics, users experience pleasure when they satisfy their opiate receptors. In psychological terms, the experience of pleasure positively reinforces drug use.

A THEORY FOR DRUG TREATMENT

It follows, then, that one way to curb drug use is to remove the positive reinforcement. The possibility of doing so hinges on what scientists call an extinction response. Again, in psychological terms, if positive reinforcement can be blocked, the interest in drug use will become extinguished. Or, more simply stated, if users find that there is no pleasurable result to be gained from drug use, they will stop using drugs.

Administering pharmacotherapeutics to elicit an extinction response in drug addicts is but one broad example of the treatment method's many applications. To be sure, this means of combating

---

[2] Roger M. Brown, *Basic Neurobiology of Addiction*, Congressional Research Service Publication, p. 4.
[3] *Ibid.*, p. 1.
[4] *Ibid.*, p. 1.
[5] *Ibid.*, p. 4.

drug addiction is controversial. Yet the arguments for it are more compelling than those against it. The discussion below will bear this out.

REASONS FOR PHARMACOTHERAPY

Pharmacotherapy demonstrates advances in science that allow for better treatment of drug abuse. This is the case for two reasons:

—First, pharmacotherapy increases the range of treatment options for drug abuse, and, thus, expands the "treatment menu" from which physicians may choose. If one treatment method is not effective, physicians may recommend other ones to their patients. The broader the range of options, the more likely recovering addicts' changes of finding one that suits them.

—Second, many different medications are available within the pharmacotherapy option itself. Just as there is tetracyclene for those who are allergic to penicillin, so too are there numerous pharmacotherapeutics for those who do not react well to their initial one.

If we can advance the cause of pharmacotherapeutic research, we can develop the medications that will enable patients to overcome their drug addictions through relatively painless and safe means.

Pharmacotherapy enhances other, more traditional methods of drug treatment. For instance, patients who pharmacotherapeutically reduce their intense craving for cocaine will be more receptive to psychological counselling and other rehabilitative services.

Pharmacotherapy also allows health care professionals to treat a larger number of drug abusers than could otherwise be accomplished using traditional therapeutic means.

Half-way houses and therapeutic communities, while potentially effective for the majority of addicts, cannot solve every addict's addiction. Dr. William Bennett, Director of National Drug Control Policy, postulates that 25 percent of the addict population is incurable given current treatment outlets.[6] Pharmacotherapy may reach that "hard-core" 25 percent. Considering Dr. Bennett's claim that there are 4 million Americans who require drug treatment, pharmacotherapy has the potential to help an extra 1 million Americans recover from their addictions.

Because pharmacotherapy is less expensive than traditional treatment methods, it stands a better chance of reaching more of the addict population. The public's treatment dollars will bring larger results.

Physicians administer pharmacotherapeutics primarily on an out-patient basis. Hospitals and treatment centers usually find bedspace the critical factor limiting treatment capacity.

The major costs of drug treatment clinics are basic to any medical establishment: the fixed costs of the building, its upkeep, the staff, and insurance premiums. Even if only for the 15 percent of their patients who receive inpatient treatment, other types of drug

---

[6] *National Drug Control Strategy*, Office of National Drug Control Strategy (Washington: GPO, 1989), p. 39.

treatment centers must pay for bedrooms, cafeterias, and other necessities of home living.

Due to long waiting lists at existing treatment programs, a significant portion of drug addicts do not receive the treatment they need.

With pharmacotherapy, which is relatively inexpensive to administer, many of those drug abusers who cannot now be accommodated may receive medical attention for their addictions.

ARGUMENTS AGAINST EXPANDING PHARMACOTHERAPY RESEARCH

As mentioned above, pharmacotherapy is a controversial subject. Despite the benefits of the treatment method, there are those who argue against expanding the use of it.

Some argue that pharmacotherapeutic drugs do nothing positive for the individuals who take them.[7] In other words, although patients might not continue to abuse illegal drugs during treatment, they would maintain the destructive attitudes and lifestyles that initiated their plight. Pharmacotherapy, the argument concludes, does nothing to correct for the deeper psychological and personality problems associated with drug use.[8]

Yet this argument does not account for the second facet of pharmacotherapeutic treatment, which is psychological counseling. By law, pharmacotherapy clinics must provide counselling to those who receive drug treatment.[9]

Opponents of pharmacotherapy also contend that it is little improvement over illegal drug use.[10] This might especially appear the case with drug maintenance therapy. The opponents explain that pharmacotherapy patients do not become drug-free, they just take different drugs.

There are three responses to this argument:

—First even, if the patients do not become drug-free immediately, pharmacotherapy provides a systematic means to their becoming so. Physicians can prescribe detoxifiers and short-term maintenance drugs that will allow patients to become drug-free with less traumatic withdrawal symptoms than experienced with current tretament methods.[11] Because the trauma can be reduced, more patients, more recovering drug addicts, can eventually reach their goal of complete detoxification.

—In the case of long-term maintenance drugs such as methadone, while the process of becoming drug-free may take longer, the pharmacotherapy patients are at least taking positive steps toward their goal.

---

[7] P.F. Renault, "Treatment of Heroin-Dependent Persons with Antagonists: Current Status," *Bulletin on Narcotics*, vol. 30. No. 2, April-June 1978, p. 23.

[8] *Ibid.*, p. 23.

[9] Department of Health and Human Services, *Federal Register*, part III, vol. 54, No. 40, Mar. 2, 1989, p. 8966.

[10] "Methadone Maintenance Treatment Remains Controversial Even After 23 Years of Experience," *Journal of the American Medical Association*, vol. 260 No. 20, Nov. 25, 1988, p. 2970.

[11] Mark S. Gold, "Opiate Withdrawal Using Clonidine," *Journal of the American Medical Association*, vol. 243, No. 4, Jan. 25, 1980, p. 343.

Methadone maintenance programs are regulated by health care professionals who can wean patients off the treatment drug by prescribing increasingly lower doses.[12]

Ceasing methadone therapy will precipitate a withdrawal syndrome, but patients will be under medical supervision and will have been able to prepare themselves through the incremental dosage reductions.

—The second response to the above argument is that drugs for drug abuse treatment are less dangerous to one's health than are illicit drugs.

Illicit drug abusers, especially of heroin, risk contracting diseases from unsafely administering the drugs. With pharmacotheraphy, health care professionals provide medications in a sterile environment.[13] There is no need for the recovering addicts to share needles and to risk catching AIDS.[14]

Illicit drugs vary in potency and may contain impurities. These variables can exacerbate the health problems that arise from illicit drug use. Such variables are not a factor with treatment drugs.

—The third reponse is that pharmacotherapy represents the controlled use of controlled substances.

—Illicit drug use is chaotic. Addicts likely will increase their habit, whereas with drug treatment the reverse will likely be true.

The regimen of taking pharmacotherapies at certain, prescribed time intervals instills a measure of order into the lives of recovering addicts.

With their lives under control and expunged of intense narcotic and cocaine action, recovering addicts can hold jobs. In general, they can begin their return to normal, productive existences.

Because they are now likely to hold jobs, and are no longer faced with the addiction-driven need to obtain large sums of money to purchase more drugs, recovering addicts are much less likely to commit violent and property crimes.

With pharmacotherapy, more addicts can be treated and their lives may become more stable. Society benefits from the increased level of stability in the addicted population through a reduction in crime rate.

Opponents of pharmacotherapy also assert that the drug treatments of the 1970's such as methadone are not applicable to the needs of today's users. Many of today's users are poly-drug users, meaning they are addicted to more than one drug. Pharmacotherapy opponents claim that it would be difficult to develop medications that could have the impact that methadone did in the 1970's because the new treatments would have to cure addicts with multiple dependencies.

---

[12] Six Federal Agency Report, "Guidance to the Use of Methadone in Maintenance and Detoxification Treatment of Narcotic Addicts," March 1989, p. 6.

[13] *Ibid.*, p. 2.

[14] Forest Tennant, *LAAM Treatment of Heroin Addiction*, Community Health Projects Group, June 1988, p. 2.

Yet while poly-drug use is a significant new challenge to pharmacotherapy, it is not an insurmountable one:

—Though it is the case that many current drug users are poly-drug users, it is also true that many of them are not. Therefore, treatments for single-drug addictions will continue to be useful.

—Yet even for these poly-drug users, there is already a treatment medication that may help them as well.[15]

Although buprenorphine is still at an early stage of development, scientists are optimistic about its effectiveness in treating addictions to both heroin and cocaine.[16]

The major drugs of abuse continue to be heroin and cocaine.[17] And drugs that may become popular, such as methamphetamine and its smokeable form "ice," are in effect similar to one of the primary drugs for which treatment methods are already available.

As will be discussed below, recent scientific evidence supports the claim that more poly-drug treatments may soon be developed.

THE FDA APPROVAL PROGESS

Perhaps the most influential opponent of pharmacotherapy is an unwitting one: "the system," or the process by which drugs receive, or do not receive, approval from the Food and Drug Administration (FDA). This report will briefly outline the long and complex process.

The Government initially requires a company to submit its proposed medication to preclinical trials. Through laboratory and animal studies, these trials assess the biological activity and safety of the medication.[18]

The Government subsequently requires that a company have its proposed treatment approved at two stages: first as an Investigational New Drug (IND), and then as a New Drug Applicant (NDA).

First, a company submits its prospective drug as an IND. At this stage, in three phases, researchers study the drug in human clinical trials.[19]

—In Phase I, researchers conduct dosage, toxicity, and low-level pharmacological tests on a group of 20 to 80 individuals.

—In Phase II, researchers conduct safety and effectiveness tests on a group of approximately 200 individuals and concentrate on the drug's treatment or prevention of a specific disease.[20]

—In Phase III, researchers "ascertain with precision the drug's safety, effectiveness, and most desirable dosage for treating a specific disease or symptom in (1000 to 3000) patients." [21]

At the successful completion of IND testing, a drug will receive FDA approval. However, before the investigation may even *begin,* the drug must have a sponsor.

---

[15] Nancy K. Mello, "Buprenorphine Suppresses Cocaine Self-Administration by Rhesus Monkeys," *Science,* vol. 245, Aug. 25, 1989, p. 859.

[16] *Ibid.*, p. 859.

[17] *NIDA Capsules,* revised August 1989 C-83-1(a).

[18] "Drug Approval Process," part of a product of the Pharmaceutical Manufacturers Association, November 1989.

[19] U.S. Department of Health and Human Services, FDA Consumer, "A Primer on New Drug Development," revised July 1981, p. 1. [HEW Publication No. (FDA) 81-3021.]

[20] *Ibid,* p.1

[21] *Ibid.*, p. 1.

NIDA funds research on most of the promising new pharmacotherapies. The Institute usually pays for half of the costs of the IND approval process. In certain instances, though, NIDA may pay for more than half of the research.[22]

It should be noted that NIDA does not need the approval of the company that owns a drug to initiate sponsorship of it as an IND.

The second stage of the drug approval process is the New Drug Application, or the NDA. "The NDA must contain all the scientific information that has been gathered. NDA's typically run 100,000 pages or more." [23]

NIDA cannot sponsor this last step that requires a private drug manufacturer to apply for a license to manufacture and distribute an IND-successful drug. This is because, while NIDA can research drugs, it cannot manufacture them. Therefore, it has no use for such a license.

This brief discussion of the FDA approval process does not reflect the vast amount of time it takes to meet the FDA's requirements. According to the Pharmaceutical Manufacturers Association, the average time it takes for a drug's development and approval is 10.5 years. Clinical testing and FDA review procedures account for 90 percent of that time.[24]

REASONS FOR THE PRIVATE SECTOR'S APPREHENSION OF PHARMACOTHERAPY

Drug manufacturers will only begin the lengthy FDA approval process if the results are likely to bring profits and enhance the company's reputation.

Unfortunately for the production of pharmacotherapeutics, the pharmaceutical industry does not often believe that drug treatments will meet either criteria. This is the case for numerous reasons.

The Pharmaceutical Manufacturers Association conducted a recent survey of its member companies "to determine the current level of research and development activity in developmental treatments for drug addiction." [25] Among other reasons, the survey found that two factors deter companies from initiating research programs into pharmacotherapeutics.

One, the scientific community currently has a limited knowledge of neuropharmacology, the study of how chemicals affect the nervous system.

And, two, companies anticipate difficulties in conducting clinical trials once their researchers discover a promising compound.

The following points reveal other potential deterrents:

Even if a treatment drug receives FDA approval, it is not likely to be profitable. The manufacturer would have to sell large quantities of it to make a profit, and the population of addicits, especially considering that not all of them will seek treatment, is small.

---

[22] Information obtained through the Legislative Affairs department of the National Institute on Drug Abuse.

[23] "Drug Approvl Process," part of a product of the Pharmaceutical Manufacturers Association, November 1989.

[24] Pharmaceutical Manufacturers Association, *Facts at a Glance*, 1987, p. 29.

[25] From a Dec. 1, 1989, letter written by the Pharmaceutical Manufacturers Association to the United States Senate Judiciary Committee.

And further, even if the addict population were large enough to warrant a company's developing a treatment drug, use of the drug would remain limited because the distribution of, and reimbursement for, (narcotic) medications are carefully controlled by the government.[26] For instance, its use may become severely restricted under the Controlled Substances Act.

And further still, even if the drug had a sufficient market and the distribution of the drug was adequate, patenting the drug might prove problematic. Certain drug treatments are too old to be patented. For instance, this is the case with LAAM, a drug to treat heroin addiction.[27]

Companies that decide to develop drug treatments or to seek pharmacotherapeutic indications for existing drugs may encounter negative publicity for their efforts. Companies fear that their reputations and the reputations of their drugs may become tainted by having drug abusers use them.[28]

According to the recent Pharmaceutical Manufacturers Association survey, the patenting and tainting issues, while persistent, are no longer a primary deterrents to companies otherwise interested in pharmacotherapeutic development.[29]

Still, the tainting phenomenon has definitely effected the research community. Scientists have not considered clinical research on drug abuse treatments a glamorous field. With little chance of notoriety or respect for their efforts, scientists tend not to devote energy to discovering and developing drugs for drug abuse treatment. This problem has slowed the progress of pharmacotherapeutic development.

As is evident from the above discussion, drug treatment manufacturers encounter difficulties with pharmacotherapeutics. The problems range from difficulties in attracting good medical researchers and developing the drugs, to getting those drugs approved by the FDA and marketed profitably. Many of the problems can be overcome, and suggestions to this end will appear in the report's final section.

II. Pharmacotherapy for Narcotics Abuse

This section of the report will present the scientific approaches that researchers use when developing pharmacotherapies for opiate addiction, and it will discuss four of the most promising opiate pharmacotherpeutics.

THEORIES OF NARCOTICS ADDICTION REVERSAL

Background

When developing medications for opiate addiction, scientists address two broad consequences of regular opiate use. First, scientists

---

[26] Robert G. Newman, "Methadone Treatment," *New England Journal of Medicine*, vol. 317, No. 7, Aug. 13, 1987, p. 449.

[27] General Policy Office, *Handbook on Drug Abuse*, 1979, p. 87.

[28] Dr. Charles Schuster, prepared testimony for an Aug. 31, 1989, hearing titled "Drugs of the 1990's: New Perils, New Promise," before the U.S. Senate Judiciary Committee, p. 4.

[29] From a Dec. 1, 1989, letter written by the Pharmaceutical Manufacturers Association to the United States Senate Judiciary Committee.

hope to halt an addict's craving for illicit narcotics.[30] And second, they attempt to minimize the ill-effects of opiate withdrawal.[31]

Narcotics addiction is brought on not only by the positive reinforcement of pleasure from using opiates, but also the negative reinforcement of pain in their absence.

Successful pharmacotherapeutics must eliminate the pleasure of drug use and the pain of withdrawal.[32]

Two terms that are relevant to the following discussion are: opiate agonists, which are drugs that produce narcotic effects, and opiate antagonists, which are drugs that block narcotic effects.

Theories

● Opiate agonists can be used as maintenance drugs. These treatments prevent the onslaught of withdrawal syndrome by satisfying the patient's opiate needs. The treatments agonists bind to and activate the same receptors as illicit agonists.

An example of an illicit agonist is heroin, and examples of treatment agonists are methadone and LAAM.

● Opiate antagonists, which may also be employed in maintenance treatment programs, are used to maintain an opiate-free state in addicts. Physicians can also use antagonists to detoxify addicts.[33] Detoxification is a necessary step for patients beginning some maintenance programs.

Antagonists work by blocking the access of agonists to opiate receptor sites.[34] With the sites blocked, agonists such as heroin can generate no pharmacological action, meaning they can produce no narcotic effect.

According to the extinction theory, if users do not receive the normally pleasurable results of narcotics self-administration they will gradually stop abusing the drug. Examples of pure antagonists are naloxone and naltrexone.[35]

● Opiate agonist-antagonists comprise the third category. Such drugs may be effective for detoxification and maintenance purposes, depending on the level of agonism or antagonism in them and the state of dependence in the patient.

This category of pharmacotherapeutic may prove useful in treatment poly-drug users. Its implications as such will be discussed in a subsequent section of this report. An example of an agonist-antagonist is buprenorphine.[36]

METHADONE

History

Perhaps the most familiar chemical treatment for drug addiction is methadone. It was the first modern drug used as a pharmaco-

---

[30] Edward G. Senay, "Methadone Maintenance Treatment," *International Journal of the Addictions*, 20 (6 and 7), 1985, p. 808.

[31] *Ibid.*, p. 808.

[32] *Handbook on Drug Abuse* (Washington: GPO, 1979), p. 91.

[33] Demetrios A. Julius, "Research and Development of Naltrexone: A New Narcotic Agonist," *American Journal of Psychiatry*, 136:6, June 1979, p. 782.

[34] *Ibid.*, p. 782.

[35] Donald R. Jasinski, "Antagonism of the Subjective, Behavioral, Pupillary, and Respiratory Depressant Effects of Cyclazocine and Naloxone," *Clinical Pharmacology and Therapeutics*, vol. 9, No. 2, 1967, p. 215.

[36] Excerpts from a NIDA Report on its proposed AIDS Budget, 1989.

therapeutic. During World War II, German scientists developed methadone as a pain-killing substitute for morphine. Yet it was not until the mid-1960's that it reached notoriety as a treatment for heroin addiction. Drs. Dole and Nyswander pioneered the methadone maintenance program in studies they conducted in the late 1960's and early 1970's.[37] The drug's FDA safety and efficacy testing as a heroin addiction treatment was conducted in the 1970's. Methadone is one of only two drugs currently approved by the FDA for drug abuse treatment; naltrexone is the other.[38] Eli Lilly produces methadone under the trade name Dolophine.[39]

Pharmacology

Methadone is a long-acting opiate agonist.[40] It produces some morphine-like effects. Administered on a regular basis, it collects in body tissues. From those tissues, it dissipates into the bloodstream at a fairly steady rate. Whereas heroin's effects last 4 to 6 hours, methadone's endure 24 to 36 hours.[41]

Dosage and Administration

Methadone is usually administered on a chronic basis, and, hence, it is often referred to as a maintenance drug. Maintenance therapy entails the regular administration of a treatment drug as a substitute for the illicit drug. In the case of methadone, as with other maintenance opiate agonists, patients must receive, at a minimum, levels of the medication sufficient to prevent the onslaught of an abstinence syndrome.[42]

If given at somewhat higher doses, methadone will also block the euphoria produced by taken heroin. Many treatment providers prefer the higher dose regimen because it not only prevents withdrawal, but it extinguishes heroin use.[43]

Methadone must be administered daily, with each dose potent enough for the entire 24-hour period.[44] Determining exactly what is too much and what is too little is a controversial process and will be discussed below.

Patients usually take methadone orally as a liquid, although oral administration carries only half the potency of intramuscular administration. Some patients may require oral doses of as much as 120 mg/day, but maintenance levels may be reduced to as little as 15 to 20 mg/day.[45]

Patients might try to reduce their maintenance levels to as little as possible, particularly when they intend to detoxify. If complete

---

[37] Edward C. Senay, "Methadone Maintenance Treatment," *The International Journal of the Addictions*, 20 (6 and 7), 1985, p. 803.

[38] *NIDA Notes*, vol. 4, No. 1, Winter 1988/1989, p. 2.

[39] Arthur J. Lewis, *Modern Drug Encyclopedia* (New York: Yorke Medical Books, 1979), p. 572.

[40] Pharmacological information from *Ibid.*, pp. 570–572; and Edward R. Barnhart, *Physicians' Desk Reference* (Oradell, N.J.: Medical Economics Co., Inc., 1989), p. 1191.

[41] *The Medical Letter*, Apr. 21, 1978, p. 40.

[42] Six Federal Agency Report, "Guidance on the Use of Methadone Maintenance and Detoxification Treatment of Narcotics Addicts," March 1989, p. 5.

[43] Reported by a member of the NIDA staff, Dec. 5. 1989.

[44] Dosage and Administration information from Arthur J. Lewis, Modern Drug Encyclopedia (New York: 1979), p. 570–572; and Edward C. Senay, "Methadone Maintenance," *The International Journal of the Addictions*, 20(6 and 7), 1985, p. 803–821.

[45] With very low doses, there is a greater risk that the treatment will fail. Recovering addicts who learn that such low doses do not block the effects heroin injections may be tempted to use the illicit drug in addition to their medication.

detoxification is their goal, some recovering addicts benefit from methadone because withdrawal from it is less acutely painful than from heroin. However, the withdrawal period is twice as long.

Adverse Effects

The methadone maintenance program is not trouble-free.[46] In addition to the opiate-style dependence it produces, methadone use may not be safe to use during pregnancies. Pregnant women who participate in methadone maintenance therapy risk methadone-dependent infants.[47] Other adverse reactions include lightheadedness, dizziness, nausea, and vomiting.

Effectiveness

Methadone maintenance programs have had a 71 percent success rate.[48] The criteria for success on which this figure is based include the recovering addicts' not using needles or abusing other drugs during two years of treatment. There are other methods of measuring methadone's effectiveness. One study that tracked the employment statistics of its participants found that 62 percent held jobs in the year subsequent to their treatment.[49] Still other studies measure success by the percentage of patients who voluntarily continue treatment. The Drug Abuse Rehabilitation Program (DARP) found that, on average, "50 percent of methadone maintenance clients were retained for one year or more and that rates of illicit opioid use and criminality decreased sharply by comparison to pretreatment rates." [50]

Controversies

There are long-standing controversies surrounding methadone treatment. It is important to note that, because methadone is the oldest and most widely used pharmacotherapeutic, it has pioneered certain controversies that might later visit other drug treatments. The issues presented below that are unique to methadone now might apply to other medications later once they, too, have been exposed to the same practical problems experienced with methadone therapy.

This report will first consider the controversies pertaining to the methods of methadone maintenance therapy.

● One issue concerns long-term versus short-term maintenance detoxification.[51] Theories differ with regard to opiate substitution programs.

—One philosophy affirms indefinite maintenance.

---

[46] Adverse effects information from Arthur J. Lewis, *Modern Drug Encyclopedia* (New York: 1979), p. 570–572.

[47] It is worth noting that methadone dependent babies are healthier than heroin addicted babies because their mothers are in treatment programs and are more likely to receive prenatal care.

[48] Timothy F. Kirn, "Methadone Maintenance Treatment Remains Controversial Even After 23 of Experience," *Journal of the American Medical Association*, vol. 260, No. 30, Nov. 25, 1988, p. 2971.

[49] Edward Senay, "Methadone Maintenance Treatment," *The International Journal of the Addictions*, 20(6 and 7), 1985, p. 804.

[50] *Ibid.*, p. 804.

[51] Theory and relevant facts presented in *Drug Abuse Treatment: A National Study of Effectiveness* (University of North Carolina Press: Chapel Hill, NC, 1989), p. 48.

—The other philosophy holds to a maintenance program of up to two years, followed by an attempt at becoming drug free.

—There is no conclusive evidence that one method is superior to the other, and federal regulations accommodate both positions.[52]

—As mentioned above, recovering addicts may choose to become completely detoxified. However, because some patients return to illicit drug use after pharmacotherapeutic treatment, indefinite maintenance might appear the best course for those not strongly motivated to become drug-free. With long-term maintenance, at least, the chance of recidivism would be reduced.

● Another issue concerns whether methadone should be available for take-home use under some circumstances.[53]

—It is possible to take the medication home and to self-administer it with ease since clinics dispense it as a liquid.

—Most States allow doctors to prescribe take-home doses for patients after three to six months of therapy.

—There are compelling reasons for this provision.

Having to go to methadone clinics every day to receive treatments is disruptive to the lives of recovering addicts.

It is time-consuming and inefficient for doctors and nurses to treat these patients on a daily basis.

Furthermore, there is the basic logistical problem of finding a means to administer the drug every day at clinics when they may close for the weekend.

—Unfortunately, a take-home system is subject to abuse and diversion.

Patients may sell their prescribed methadone on the street for the money they need to buy more "desirable" drugs such as crack or heroin.[54] The more methadone that is taken from the clinics, the larger the potential illicit market in the drug.

In sum, patients who sell their methadone do not become cured, let alone maintained, and a new illicit market for drugs is created.

However, as Dr. Robert Newman at Beth Israel Medical Center indicates, there are two sides to the illicit market phenomenon. While patients might sell their methadone maliciously, those who buy it might do so for understandable reasons. The buyers might be addicts who have been "forced to languish on waiting lists" at treatment clinics.[55] In other words, the buyers may want the methadone for its drug treatment benefits, not its narcotic effects.

● A third controversy involves determining the proper dosage levels for methadone.

---

[52] Six Federal Agency Report, "Guidance on the Use of Methadone Maintenance and Detoxification Treatment of Narcotic Addicts," March 1989, p. 7.

[53] The issue and relevant facts are presented in *Drug Abuse Treatment: A National Study of Effectiveness* (Chapel Hill: 1989), p. 51-52.

[54] Michael Isikoff, "Abuse, Trafficking Found in Methadone Clinics," *Washington Post*, Aug. 3, 1989, p. A3.

[55] From a Nov. 27, 1989, letter written by Dr. Robert Newman at Beth Israel Medical Center to the U.S. Senate Judiciary Committee.

—Researchers and physicians have never established a normative range of dosing.[56] Under current procedures, doctors have a great deal of leeway to decide what is the correct level for each patient.

—This controversy has led to problems that involve doctors as well as patients.

With regard to the doctors:

Methadone clinic operators make more money when they dispense larger amounts of methadone. For instance, some states provide methadone to patients through the Medicaid system.

Since most patients do not pay for their visits to the clinics, the sole source of income for the treatment centers is the reimbursement they receive for methadone allocations.

Of course, even in cases where patients pay for their methadone, doctors might over-prescribe for the same reasons.

The problem, then, is that doctors might spend minimal amounts of time at their clinics and prescribe larger than necessary doses of methadone to increase their profits.[57]

With regard to the patients:

Safeguards to prevent diversion and over-prescription may harm patients. They may ask for increased doses of methadone because they truly need it to avoid an abstinence syndrome, not to feed the illicit market.

Or they may only pretend to need the methadone, figuring instead to sell it on the illicit market.

In light of the illicit market for methadone that is fed when wrong decisions are made, this controversy becomes all the more important to resolve.

● There are two more major controversies surrounding the methods of dispensing methadone, although only one of them is unique to the drug. The unique controversy concerns interim maintenance programs.[58]

—Recently, some have suggested allowing patients to receive methadone from clinics without the normally prescribed accompanying psychotherapy and counselling.

—The controversial interim program would allow clinics to counsel patients about AIDS transmission and then provide doses of methadone without any further counselling. The interim patients would be put on a list and, when general counselling slots become available, they would be admitted to the sessions.

—No one denies that pharmacotherapy is more effective when it is administered in conjunction with psychotherapy. Nonetheless, counselling a patient is much more costly and time-consuming than administering a drug.

---

[56] Theory and relevant facts presented in *Drug Abuse Treatment: A National Study of Effectiveness* (Chapel Hill: 1989), p. 50–51.

[57] Thomas J. Maier, "The Business of Addiction: Two Treatments," *Newsday*, Business Section, June 12, 1989, p. 9.

[58] The issue and relevant facts are in *Summary of the Federal Register*, Mar. 2, 1989, p. 1; and *Drug Abuse Treatment: A National Study of Effectiveness* (Chapel Hill: 1989), p. 52–55.

—Proponents of interim periods argue that:

There are often long waiting lists at methadone clinics of addicts who seek treatment. These lists grow because of the psychotherapy side of the treatment program.

The interim program would allow many more drug addicts to receive the treatment they seek. And the drug medications are not wholly ineffective when administered without psychotherapy.

Anyway, interim patients would ultimately receive full treatment.

—Opponents of this interim method contend that it defeats the original purpose of methadone maintenance therapy for two reasons.

First, it may contribute to a larger illicit market for methadone. Patients would have little trouble entering methadone clinics and receiving doses of the drug. Without the proper counseling and monitoring, addicts might easily return to illicit drug use while continuing to use the methadone clinic as an indirect source of drug money.

Second, some contend that psychotherapy and practical counselling are so essential to the drug treatment process that it is senseless, if not detrimental, to supply patients with methadone in the absence of such counselling.

● The final controversy concerns urinalysis and the privacy rights of methadone patients.[59]

—Despite the efficacy of pharmacotherapeutics, patients may continue to abuse drugs while in treatment.[60]

—Urinalysis is one way to monitor the progress of patients and to ensure their compliance with the treatment program.

—However, many contend that subjecting recovering addicts to such tests is a violation of their right to privacy.

The above discussion concerned controversies over methadone maintenance therapy practices. Still to be discussed are the controversies over whether methadone is the best heroin substitute.

● One issue has already been mentioned in this report: methadone has spawned an illicit market.[61] This problem could be corrected in two ways:

—One, a new maintenance drug could be marketed that has opiate antagonist properties. Such a drug, like buprenorphine, would not produce the level of opiate agonist effects observed with sporadic methadone use. Without a high level of narcotic action, buprenorphine would generate less demand on the illicit market.

—And, two, a new drug could be marketed that has the opiate agonist properties found in methadone but a slower onset of action. LAAM is such a drug.[62] LAAM is slow-acting enough

---

[59] The issue and relevant facts are in *Drug Abuse Treatment: A National Study of Effectiveness.* (Chapel Hill: 1989), p. 51.

[60] Michael Isikoff, "Abuse, Trafficking Found in Methadone Clinics," *Washington Post,* Aug. 3, 1989, p. A3.

[61] Timothy F. Kirn, "Methadone Maintenance Treatment Remains Controversial Even After 23 Years of Experience," *Journal of the American Medical Association, Vol. 260,* No. 20, Nov. 25, 1988, p. 2975.

[62] Elaine Karp-Gelernter, "Evaluation Clinic Attendance Schedules for LAAM and Methadone: A Controlled Study," *The International Journal of the Addictions,* 17(5), 1982, p. 806.

that its opiate properties would be barely apparent to recovering addicts. Because LAAM use does not elicit a significant "high," it would not likely generate a large illicit market.

- Another concern with methadone is that it is addictive.

—A drug with less abuse potential, such as buprenorphine, could replace methadone. Buprenorphine may produce some psychological dependence, but withdrawal from it is shorter and less intense than withdrawal from either heroin or methadone.[63]

- A potential drawback of methadone is that it requires daily administration.

—If recovering addicts must go to clinics to receive their daily doses, they may have difficulty finding steady work. The addicts would have to excuse themselves from their job every day, causing lost production hours.

—Also, such a schedule keeps recovering addicts in daily contact with other drug users who may pressure or entice them into recidivism.[64]

—Furthermore, methadone maintenance programs keep patients in the habit of taking drugs every day.[65]

—LAAM again, could be a valid substitute. The three-day duration of its opiate agonist action would lessen all of these problems.

It is important to note that, as described in the above examples, the drawbacks of one medication such as methadone may be corrected by prescribing other pharmacotherapeutics. One would hope that in the future there will be a number of such agents to choose from, depending on the problems raised by individual patients.

LAAM

History

Around 1948, scientists in Germany developed LAAM, Levo-Alpha Acetylmethadol, as an analgesic.[66] Despite its early discovery, LAAM, like methadone, did not emerge as a potential treatment for drug abuse until the late 1960's. Since then, LAAM has been caught in a complex struggle that pits the drug's apparent effectiveness against the realities of the pharmaceutical industry.

Dr. Jerome Jaffe was an early pioneer in the testing and use of LAAM as a pharmacotherapeutic for narcotics abuse.[67] The drug's initial trials as a pharmacotherapeutic were so successful that at one point the Nixon administration predicted it would be available for prescription use by 1974. However, phase II studies were not initiated until 1973 and not completed until 1976. And phase III testing did not begin until the late 1970's.[68] LAAM has satisfied most of the Phase III testing requirements, and scientists have accumulated a great deal of statistical information about the drug,

---

[63] J.H., "Lukewarm Turkey," *Scientific American,* March 1989, p. 32.

[64] The White House Conference for a Drug Free America, "Final Report," June 1988, p. 78. To the extent that visits to a methadone clinic place patients in regular contact with counselors, the daily requirement may also have a positive indirect effect on recovering addicts.

[65] Although methadone patients take their medication daily, it is important to note that they do so orally, which helps them to break the habit of using needles.

[66] *Handbook on Drug Abuse,* (Washington: GPO., 1979), p. 87.

[67] *Ibid.,* p. 88.

[68] *Ibid.,* p. 91.

but it has not yet successfully completed this phase of the IND process.

No company has yet applied to sponsor LAAM through the remainder of its IND testing nor to own it for manufacturing purposes. In the meantime, LAAM is publicly owned. Finding a private sponsor for it is an immediate priority at NIDA.[69] NIDA's initiatives in this area and the issues that prompted the Institute's involvement will be discussed below.

Pharmacology

Chemically, LAAM resembles methadone.[70] It is a longer-lasting opiate than methadone, though; its effects endure for 48 to 72 hours.[71] When administered to people who are not tolerant to opiates, LAAM produces typical narcotic effects, including analgesia and somnolence.[72] Yet the effects occur with a slower onset of action than they do with methadone. The onset takes hours and the effects, once noticed, are sustained but weak. LAAM does carry the potential of overdose.[73] Still, LAAM is a narcotic agonist, and opiate antagonists such as naloxone can reverse its narcotic action. Thus, instances of overdose may be treated.

Dosage and Administration

Scientists have found that the guidelines for choosing methadone patients are applicable to the selection process for LAAM patients.[74] Because of LAAM's unique long-acting property, it needs to be administered only three times a week. Traditionally, the 3 days are Monday, Wednesday, and Friday, with a larger than usual dose given on Friday to satisfy the patient through the weekend.[75] While these 3 days are traditional, clinics and patients may choose any 3 days that respect the appropriate time intervals.

Many of the patients who have been maintained on LAAM were at one time maintained on methadone. There is no optimal crossover schedule established for patients who either transfer from methadone therapy or begin pharmacotherapy with LAAM. Still, one report suggests using a crossover ratio of 1.0 to 1.3 mg LAAM three times a week for each milligram of daily methadone.[76] The target stabilization dose with LAAM is 80 mg.[77] Still, as in methadone maintenance therapy, doses should be prescribed on a patient-by-patient basis.

Adverse Effects

Therapy with LAAM includes a range of adverse side effects that are typical of opiate agonists.[78] LAAM tests in human subjects

---

[69] *ADAMHA News*, vol. 15, No. 3, May 1989, p. 19.
[70] "Test of Alternative to Methadone Is Set," *The New York Times*, Jan. 9, 1978, p. A28.
[71] "New Drugs May Make Methadone Obsolete," *The Washington Post*, June 4, 1981, p. C3.
[72] *The Medical Letter*, Apr. 21, 1978, p. 40.
[73] *Ibid.*, p. 40.
[74] *Handbook on Drug Abuse* (Washington: GPO., 1979), p. 93.
[75] Elaine Karp-Gelernter, Evaluation of Clinical Attendance Schedules for LAAM and Methadone: A Controlled Study," *The International Journal of the Addictions*, 17(5), 1982.
[76] *Handbook on Drug Abuse*, (Washington: GPO., 1979), p. 93.
[77] *Ibid.*, p. 93.
[78] *The Medical Letter*, Apr. 21, 1978, p. 40.

have yielded no major adverse health consequences, but similar tests in laboratory rats have linked the drug to liver cancer. This is a major reason why the FDA has never approved the drug for general use. However, it now appears that LAAM's carcinogenic effects was overstated.

Effectiveness

Researchers measure LAAM's effectiveness comparatively. They test their patients' preference for LAAM over methadone. In other words, methadone has emerged as a standard for success. And on that standard, LAAM fares well. One study found that 50 percent of its subjects chose to remain enrolled in LAAM maintenance programs rather than to return to methadone therapy. A later study found that percentage to be as high as 89 percent.[79]

Controversies

Despite the impressive statistics, LAAM is not without its share of controversies.

● First, there are controversies surrounding the drug's legal status. As mentioned above, LAAM is owned by the public and is not manufactured by any private company.

—At issue is the fact that LAAM is too old to patent.[80]

—Potential manufacturers, who already have little interest in treatment drugs, are not eager to finance the development of one that cannot be patented.

If a company were to develop such a drug, competitors could produce it generically. This would result in the division of an already marginally profitable market.

The original manufacturing company would then not be able to recoup the resources used to develop the drug and would not realize a profit for the efforts and risks taken in producing it.

● A second issue in LAAM's development concerns the formula for the drug.

—Apparently, only one batch of LAAM has been made in the United States.

—There is skepticism in the pharmaceutical industry about whether LAAM can be produced profitably on the basis of one, untested formula.

● Some are also skeptical about LAAM as a viable and efficacious treatment for narcotics addiction.

—LAAM treatment trials have had difficulty keeping patients enrolled.[81] According to one report, the tendency for greater therapeutic yield with methadone as compared to LAAM has been often observed through little noted.[82].

—Yet Dr. Forest Tennant argues that LAAM treatment trials do not suffer from enrollment problems. He claims that, actually, LAAM brings more addicts to therapy than does methadone.

---

[79] *Handbook on Drug Abuse* (Washington: GPO., 1979), p. 94; and "Narcotic Substitute," *U.S. Medicine*, May 1, 1978, p. 1.

[80] *Handbook on Drug Abuse* (Washington: GPO, 1979).

[81] Elaine Karp-Gelernter, "Evaluation of Clinic Attendance Schedules for LAAM and Methadone: A Controlled Study," *The International Journal of the Addictions*, 17(5), 1982, p. 812.

[82] *Ibid.*, p. 812.

—Even if Dr. Tennant is wrong, LAAM would still be a valuable treatment medication.

One, LAAM could be the necessary substitute for methadone. Physicians agree that one drug does not suit all patients. Therefore, those who do not benefit from methadone for any number of reasons will require a substitute drug, and LAAM is a reasonable replacement.

And, two, patients who withdraw from LAAM treatment programs often switch to methadone maintenance therapy, but the converse has not been found to be true.[83] With LAAM, then, and not with methadone, patients potentially have two chances at stabilizing their addictions.

● The slow-starting nature of LAAM's narcotics effects can be a great asset.

As noted above, LAAM produces such a delayed and weak "high" that there is little chance of its becoming popular on the street and spawning an illicit market.[84]

Thus, if it ever were prescribed on a take-home basis, one of the problems associated with take-home methadone would not be duplicated.

● Unlike methadone, however, LAAM may never provoke a controversy over clinical versus take-home administration because of its extended duration of action. The drug needs to be taken only three times a week

—If LAAM stays in clinics, this further reduces the chance that it will be diverted and sold illegally, and the realistic chance of overdose would be slight.

—Treatment with LAAM would incur less interference with school and employment than would daily methadone.

—And, compared again to daily methadone, LAAM would lead to less patient preoccupation with drugs and drug taking.

NALOXONE

History

Naloxone was available as an opiate antagonist long before it was incorporated into drug treatment programs in the early 1970's.[85] The drug, which is owned by Endo and sold under the trade name Narcan, is now approved by the FDA "for short-term used in humans as an antidote to opiate overdose." [86] This may be the only approved indication, but naloxone has since become widely used as an effective detoxifier.

Pharmacology

Naloxone is a pure narcotic antagonist; it blocks narcotic action. As a pure antagonist, it possesses none of the agonist, or morphine-

---

[83] *Handbook on Drug Abuse* (Washington: GPO, 1979), p. 90.

[84] *The Medical Letter*, Apr. 21, 1978, p. 40.

[85] Demetrios A. Julius, "Research and Development of Naltrexone: A New Narcotic Antagonist," *American Journal of Psychiatry*, 136:6, June 1979, p. 784.

[86] *NIDA Notes* vol. 4, No. 1, Winter 1988/1989, p. 5; and Edward R. Barnhart, *The Physicians' Desk Reference* (Oradell, N.J.: 1989), p. 910.

like, properties of partial narcotic antagonists such as buprenorphine.[87]

Naloxone antagonizes opiate effects by competing for the same receptor sites in the brain as do opiate agonists.[88] In addition to reversing opiate overdose, naloxone may be used as a rapid means to detoxification. One study reports that naloxone can detoxify patients in one to two days.[89]

Naloxone provides an example of how opiate antagonists may be used to moderate the transition of recovering addicts from illicit drug use to treatment programs. Naloxone acts as a precursor to therapeutic agents that require initial detoxification. Clonidine might also be used to suppress withdrawal symptoms in patients beginning pharmacotherapeutic treatment with naltrexone.[90]

Dosage and Administration

Naloxone may be administered intravenously, intramuscularly, and subcutaneously.[91] The initial dose is usually 0.4 mg. This dosage is repeated every two to three minutes, or until the desired effects are achieved. Naloxone may also be taken orally, but it is significantly less potent when administered that way. Naloxone treatment requires much professional supervision. The drug has no clinical history of overdose in humans.[92]

Adverse Effects

Nausea and vomiting are typical of opiate reversals, such as from the agonist morphine to the antagonist naloxone.[93] Although naloxone produces a full-blown withdrawal syndrome in people dependent on opiates, there are few cases of naloxone's provoking unique adverse effects in drug-free patients. Specifically, it does not appear that naloxone adversely effects pregnant women and their fetuses. Clinical research on humans, however, is not complete.

Effectiveness

In a sense, naloxone's success as a detoxifier is guaranteed. It is a pure antagonist, and in 100 percent of the cases it will block narcotics action. Another measure of naloxone's success concerns the speed with which it can detoxify recovering addicts. One study published in *Clinical Pharmacology and Therapeutics* reported finding both and 1- and 2- day naloxone-precipitated detoxification programs. The 1-day program is the quickest safe method known with an FDA-approved drug.[94]

---

[87] Donald R. Jasinski, "Antagonism of the Subjective, Behavioral, Pupillary, and Respiratory Depressant Effects of Cyclazocine by Naloxone," *Clinical Pharmacology and Therapeutics*, vol. 9, No. 2, 1967, p. 215.

[88] Edward R. Barnhart, *The Physicians' Desk Reference* (Oradell, N.J.: 1989), p. 911.

[89] Richard B. Resnick, "Naloxone-Precipitated Withdrawal: A Method for Rapid Induction onto Naltrexone," *Clinical Pharamacology and Therapeutics* , vol. 21, No. 4, 1976, p. 409.

[90] Dennis S. Charney, "The Combined Use of Clonidine and Naltrexone as a Rapid, Safe, and Effective Treatment of Abrupt Withdrawal from Methadone," *American Journal of Psychiatry*, 143:7, July 1986, p. 831.

[91] Information about administration in Edward R. Barnhart, *The Physician's Desk Reference* (Oradell, N.J.: 1989) p. 912.

[92] *Ibid.*, p. 912.

[93] Information on adverse effects in Edward R. Barnhart, *The Physicians' Desk Reference* (Oradell, N.J.: 1989) p. 911-912.

[94] Richard B. Resnick, "Naloxone-Precipitated Withdrawal: A Method for Rapid Induction onto Naltrexone," *Clinical Pharmacology and Therapeutics*, vol. 21, No. 4. 1976, p. 412.

Controversies

Naloxone may serve a valuable function by providing a necessary, quick method of detoxification with less total discomfort than that experienced with longer, more gradual withdrawal.[95] Yet there are problems with it.

—Naloxone is expensive and difficult to synthesize.

—Also, it has a poor oral absorption rate and a extremely short duration of action.[96]

Naltrexone was introduced to respond to these problems in treating opiate addiction.

NALTREXONE

History

Naltrexone is a pure antagonist, and was developed for the treatment of narcotics addiction in the early 1970s.[97] From 1973 to 1974, the National Institute on Drug Abuse and the Special Action Office for Drug Abuse Prevention (SAODAP) shared the responsibility for developing naltrexone.[98] Once SAODAP was disbanded in 1974, full responsibility for the task fell on the NIDA Division of Research. By 1974, naltrexone had entered phase II testing. At its successful completion of phase II, NIDA requested that DuPont, the drug's owner, sponsor naltrexone through the final testing stage, phase III.

However, the phase III testing was subsequently deemed unnecessary and was curtailed.[99] In 1984, the FDA approved naltrexone for manufacture and prescription use. DuPont sells it under the trade name Trexan.

Since the drug's approval, NIDA has been working on a hybrid of it known as a depot form.[100] Depots are implanted under the skin, allowing the drug to dissipate gradually into the blood stream. This form of ingestion lengthens the drug's duration of action. In the case of naltrexone, the action may be extended to a month.

Pharmacology

As mentioned above, naltrexone is an opiate antagonist; it blocks the narcotic action and dependence-producing properties of opiate agonists. Its chemical structure is similar enough to opiate agonists that it can occupy the same receptor sites that true agonists would otherwise occupy.[101] When the agonists are not able to bind to the proper receptors in the brain, narcotic effects cannot be experienced.

---

[95] Charles Riordan and Herbert Kleber, "Rapid Opiate Detoxification with Clonidine and Naloxone," *The Lancet*, May 17, 1980, p. 1079.

[96] Demetrios A. Julius, "Research and Development of Naltrexone: A New Narcotic Antagonist," *American Journal of Psychiatry*, 136:6, June 1979, p. 784.

[97] *Ibid.*, p. 784.

[98] *Ibid.*, p. 784.

[99] Information obtained from the DuPont Co., Public Affairs Office.

[100] *NIDA Notes*, vol. 4, No. 1, Winter 1988/1989, p. 5.

[101] Demetrios A. Julius, "Research and Development of Naltrexone: A New Narcotic Antagonist," *American Journal of Psychiatry*, 136:6, June 1979, p. 782.

Naltrexone has few if any pharmacological effects besides its opiate blocking property. Unlike methadone, naltrexone is not addictive.[102]

Dosage and Administration

Naltrexone precipitates an abstinence syndrome in patients who are not fully detoxified before treatment.[103] To minimize the chances of experiencing withdrawal, patients must participate in an elaborate screening system.[104] Patients should abstain from narcotics for at least 7 to 10 days before taking naltrexone. During this time, complete detoxification should occur.

As a final precaution, though, patients should receive a "naltrexone test" consisting of a relatively small dose of 25 mg. If they pass the "test," meaning if abstinence syndrome does not set in, they will receive doses of 50 mg each weekday and 100 mg on Saturdays. With good patient response, doses may be increased so that physicians need administer them only every 48 to 72 hours. There are no known incidences of overdose with naltrexone.[105]

Adverse Effects

When given to the proper patients, detoxified formerly opioid-dependent individuals, there is no single, serious outward risk incurred from naltrexone use.[106] Nonetheless, patients may experience some minor side effects.

There are only incomplete studies on the effects naltrexone has on pregnant women, their fetuses, labor, and delivery.[107] Also, it is unclear the extent to which naltrexone is present in the milk of nursing mothers.

Effectiveness

Naltrexone can be very effective. Scientists measure its effectiveness in terms of the number of patients who can withdraw successfully from maintenance therapy or illicit narcotics abuse. In one study that caused clonidine to moderate withdrawal symptoms, naltrexone was 95 percent successful in treating subjects for addiction to methadone.[108]

Controversies

As with the other narcotics treatments, naltrexone has its detractors.

- The attendance or compliance rate of patients in naltrexone studies has been low, which may indicate dissatisfaction with the method of treatment and the drug itself.[109]

---

[102] Edward J. Callahan, "The Treatment of Heroin Addiction: Naltrexone Alone and with Behavior Therapy," *The International Journal of the Addictions*, 15(6), 1980, p. 797.

[103] P.F. Renault, "Treatment of Heroin-Dependent Persons with Antagonists: Current Status," *Bulletin on Narcotics*, vol. 30, No. 2, April-June 1978, p. 25.

[104] Edward R. Barnhart, *The Physician's Desk Reference* (Oradell, N.J.: 1989), p. 919.

[105] *Ibid.*, p. 918.

[106] Demetrios A. Julius, "Research and Development of Naltrexone: A New Narcotic Antagonist," *American Journal of Psychiatry*, 136:6, June 1979, p. 785.

[107] Edward R. Barnhart, *The Physicians' Desk Reference* (Oradell, N.J.: 1989), p. 918-919.

[108] Dennis S. Charney, "The Combined Use of Clonidine and Naltrexone As a Rapid, Safe, and Effective Treatment of Abrupt Withdrawal from Methadone," *American Journal of Psychiatry*, 143:7, July 1986, p. 831.

[109] P.F. Renault, "Treatment of Heroin-Dependent Persons with Antagonists: Current Status," *Bulletin on Narcotics*, vol. 30, No. 2, April-June 1978, p. 26.

—Confirming this, recent clinical reports reveal taht naltrexone, although available, is not wanted by the addict population seeking treatment.
—In a sense, such problems arise because naltrexone works too well. It is highly effective at blocking the pleasurable feelings that addicts associate with narcotics use.
—If a treatment menu is available, often patients will opt for opiate agonists for what little "high" they provide. No doubt, treatment patients figure that some measure of opiate action, especially in the legal context of recovering from drug abuse, is more desirable than no narcotic action whatsoever.
—Studies may have problems with compliance, and clinics with patients not choosing naltrexone, for this reason.

● Another positive facet of naltrexone, its non-addictive nature, presents a surprising drawback.

—With addictive drugs such as methadone, at least the patients' addiction, if not their better judgment, will keep them enrolled at clincs.
—There is no such built-in compliance mechanism with naltrexone. Use of naltrexone for long-term maintenance requires addicts who are very dedicated to staying off drugs.
—Still, many would argue that is better for addicts to be treated to some extent than for them not to be treated at all. Even if addicts do not complete their therapy, they will at least have become sober for some length of time.

III. Pharmacotherapy for Cocaine Abuse

In the 1980's, the scientific community has come to view cocaine as an addictive substance. And in the last 5 years, America's experience with the increasing crack cocaine problem has corroborated the new scientific opinion. Partly because these scientific and social perceptions have changed only recently, research on treatments for cocaine abuse is at a fledging stage.

THEORIES OF COCAINE ADDICTION REVERSAL

Background

There are many promising medications now being tested, but none have been approved by the FDA for treating drug addiction.[110] In fact, the medications are generally in the early stages of development. However, as the examples in this section will illustrate, most of the drugs under consideration for cocaine abuse treatment are ones that have FDA approval for other illnesses or conditions.

Numerous durgs are currently being studied for their effectiveness in treating cocaine abuse; NIDA itself funds the research for 19.[111] To date, the most promising drug treatments for cocaine addiction have been anti-depressants. These medications appear to reduce the intense craving for cocaine that addicts experience during withdrawal.

---

[110] *NIDA Notes*, vol. 4, No. 1, Winter 1988/1989, p. 5.
[111] *Ibid*, p. 5.

This report will discuss three prospective treatments. These medications illustrate theories of cocaine addiction treatment that will be presented below.

Theories

As mentioned at the beginning of this report, researchers are now concentrating on the brain reward circuitry hypothesis of addiction. Essentially, the hypothesis holds that people use an illicit drug because the effects are pleasurable, and that pleasure reinforces behavior. Once people feel the euphoria or "high" that they can derive from a drug such as cocaine, they will continue to seek it out and use it. In other words, they will crave it.

Cocaine is immediately reinforcing—users experience positive effects from the drug the first time they use it.[112] Studies have shown that cocaine use is so self-reinforcing that animals will often ignore their basic biological drives for food and sleep in favor of continued cocaine use. In fact, they will ignore their basic drives until they collapse and die.

Obviously, drug users do not begin using drugs with the intention of becoming addicted. Yet, considering the powerful reinforcing effects of cocaine, abuse often leads an intense craving for the drug. Once such craving begins, the drug abuser has become addicted.

Researchers hope that they can help addicts by addressing this craving factor.

As research into cocaine addiction is still in its infancy, little is known about the specific physiological mechanisms that induce the craving, but many believe that the root causes lie in neurotransmission. Neurotransmission is the body's means of transplanting experiences into sensations.

The three most significant neurotransmitters with regard to cocaine treatment are:

(1) Dopamine, which is responsible for the sensation of pleasure;

(2) Serotonin, which is responsible for the anxiety reflex; and

(3) Norepinephrine (noradrenaline), which is responsible for the fear reflex.

These three neurotransmitters are also known as monoamines.

It bares repeating that, due to the limited amount of well-documented research in the area of cocaine addiction, researchers are only at the stage that they can demonstrate that certain drugs works or do not work. So, while the drugs may help patients to stop using cocaine, researchers do not necessrily know why the medications have such positive effects.

Researchers hypothesize, however, that the promising medications discussed below will counter the effects of cocaine on neurotransmission—perhaps by altering the production or reception of dopamine—and thus reduce the pleasurable effects of, and the craving for, cocaine.

---

[112] Roger M. Brown, *Basic Neurobiology of Addiction*, Congressional Research Service Publication, p. 3.

IMIPRAMINE

History

Imipramine has been available to scientists at least since the early 1970's, and has been approved by the FDA for the treatment of depression.[113] NIDA provides funding for pharmacotherapeutic research on imipramine, which is at the equivalent of an IND's phase II testing.[114] Geigy, a pharmaceutical company, owns the drug and sells it under the trade name Tofranil.

Imipramine is an example of a drug that the FDA has approved for a certain indication but which scientists are discovering has additional potential as a pharmacotherapeutic.

Pharmacology

Imipramine is chemically related to desipramine, another tricyclic that scientists have found effective in the treatment of cocaine addiction.[115] The term "tricyclic" refers to the three fused rings in the drug's chemical structure. Like other tricyclics, imipramine is not habit forming.[116] Its mechanism of action is not clear, although scientists suspect that it prevents re-uptake of monoamines such as norepinephrine and serotonin.[117]

The following will describe the concept of "re-uptake" using the neurotransmitter dopamine as an example: For the body to sense pleasure, its neurons must release dopamine. Given the proper stimulus, dopamine will be released into synapses, dopamine will induce adjoining neurons to release their supplies of the neurotransmitter.

Normally, this process continues as a chain reaction until sufficient amounts of dopamine are released for people to sense the amount of pleasure they usually associate with the original stimulus.

The release of dopamine would continue unchecked if there were no mechanism for either neutralizing the neurotransmitter in the synapses or bringing it back into the neurons to cease its perpetual triggering of other neurons. Re-uptake is the process by which neurons recover their released neurotransmitters from nearby synapses.[118]

The consequence of re-uptake, then, is the limitation, and eventual reversal, of the effects of a given neurotransmitter. By preventing the re-uptake of fear and anxeity neurotransmitters such as serotonin and norepinephrine, tricyclics have a soothing effect on those who take them. In this way, they act as antidepressants.

Researchers hope that the antidepressant effects of tricyclic such as imipramine will help addicts through the doldrums that accompany cocaine withdrawal.

---

[113] Arthur J. Lewis, *Modern Drug Encyclopedia* (New York: 1979), p. 462.
[114] *NIDA Notes*, vol. 4, No. 1, Winter 1988/1989, p. 5.
[115] Robert Wilbur, "A Drug To Fight Cocaine," *Science*, March 1986, p. 44.
[116] *Ibid.*, p. 44.
[117] Arthur J. Lewis, *Modern Drug Encyclopedia* (New York: 1979), p. 462.
[118] Robert Wilbur, "A Drug to Fight Cocaine," *Science*, March 1986, p. 44.

Adverse Effects

The drug's manufacturer lists several adverse effects for imipramine.[119] The list warns that it should only be used on pregnant and nursing women if the potential benefits outweigh the possible hazards to the mother and child.

Effectiveness

Statistics on the effectiveness of imipramine are not available. However, desipramine, another tricyclic, has proven 60 percent successful in significantly reducing an addict's craving for cocaine.[120]

DILTIAZEM

History

For many years, doctors have prescribed diltiazem as a treatment for angina.[121] Sold under the trade name Cardizem, it is manufactured by Marion Laboratories. NIDA provides funding for pharmacotherapeutic research on diltiazem, which is at the equivalent of an IND's animal testing stage of development.[122]

Pharmcology

Diltiazem is a calcium channel blocker. Nifedipine and Verapamil are other examples of calcium channel blockers, which stem the flow of calcium ions across the plasma membrane of neurons.[123]

The mechanics and implications of this fact are as follows: neurons store their respective neurotransmitters in vesicles. The vesicle contents remain inside the neuron's cell wall until chemically released into synapses. The necessary chemical reaction results from the influx of calcium into the neuron.

Calcium, thus, is integral to interneural transmission. For example, the neurotransmitter of dopamine requires the flow of calcium into dopaminergic neurons. As a calcium channel blocker, diltiazem curtails the flow of the ion calcium into neurons.

Because cocaine-induced euphoria follows partly from the release of dopamine in pleasure circuits of the brain, a depot form of diltiazem might reduce the illicit drug's pleasurable effects. Consequently, the treatment may elicit an extinction response in recovering addicts. In other words, in the absence of positive reinforcement, users may cease to abuse cocaine.

Calcium channel blockers may benefit cocaine abusers in another way. As mentioned above, the blockers were originally developed to treat heart ailments. In that vein, they may also help reduce cocaine-related heart problems such as cardiac cardio-toxicity.[124]

---

[119] Information on warnings and adverse effects in Arthur J. Lewis, *Modern Drug Encyclopedia* (New York: 1979), p. 462–463.

[120] Deborah Barnes, "Breaking the Cycle of Addiction," *Science*, vol. 241, Aug. 26, 1988, p. 1029.

[121] Edward R. Barnhart, *Physicians' Desk Reference* (Oradell, N.J.: 1989), p. 1215.

[122] *NIDA Notes*, vol. 4, No. 1, Winter 1988/1989, p.5.

[123] Gerhard J. Johnson, "Disparate Effects of the Calcium-Channel Blockers, Nifedipine and Verapamil, on a_2-adrenergic receptors and thromboxane A_2-induced aggregation of human platelets," *Circulation*, vol. 73, Number 4, April 1986, p. 847.

[124] *NIDA Notes*, vol. 4, No. 1, Winter 1988/1989, p. 5.

Simply stated, the medications help the heart to slow down and, thus, not to exhaust its oxygen supply.

Adverse Effects

With diltiazem,there is also the possibility of severe adverse reactions such as heart failure and amnesia, but these instances are very rare.[125] Various minor side effects such as headaches and rashes occur slightly more frequently.

Effectiveness

Diltiazem and other calcium channel blockers are in too early a stage of development as drug medications for their effectiveness to be well documented.

CARBAMAZEPINE

History

Carbamazepine has been used since the early 1960's to control convulsions in epileptics.[126] It also has analgesic properties. Recently scientists have suspected that it has still wider applications. In the 1980's, for instance, researchers have experimented with its use as an alternative to lithium for curbing the aggressive behavior of violent patients.[127]

Carbamazepine, sold under the trade name Tegretol, is owned by Geigy. NIDA provides funding for pharmacotherapeutic research on carbamazepine, which is at the equivalent of an IND's phase II testing. Further testing of carbamazepine for its pharmacotherapeutic value is a high priority at NIDA.[128]

Pharmacology

Carbamazepine is structurally similar to tricyclic antidepressants.[129] While researchers are not certain about how the drug works, one theory suggests that carbamazepine's effectiveness as a treatment for epileptic seizures may hold the key to its success as a cocaine abuse medication.[130]

Epileptics may experience seizures due to spontaneous, massive electrical discharges in their brains. These seizures apparently result after the slow buildup of electrical energy.

Repeated exposure to low doses of cocaine may culminate in seizures of craving. Dr. James Halikas theorizes that these seizures are the behavioral manifestations of the same sort of electrical buildup that epileptics experience.[131] Just as carbamazepine prevents seizures in epileptics, so too might it reduce cocaine induced craving.

---

[125] *Ibid.*, p. 1216.
[126] *USA Today*, February 1985, "Your Health" Section, p. 11.
[127] *Ibid.*, p. 11.
[128] Information obtained from NIDA's legislative affairs office.
[129] Arthur J. Lewis, *Modern Drug Encyclopedia* (New York: 1979), p. 143.
[130] Summary of a clinical study by Dr. James Halikas of the University of Minnesota.
[131] Abstract for Dr. Halikas' poster at the American Psychopathological Association.

Adverse Effects

Carbamazepine has many potential side effects, some of them serious.[132] For instance, there is a small chance of heart failure or liver dysfunction from taking the drug. Other potential adverse effects are more mild; they inlcude nausea, vomiting, dizziness, and headache.

Effectiveness

Studies using carbamazepine as a pharmacotherapeutic, particularly at the University of Minnesota, have found the medication effective. In one open, self-reporting study, 33 percent of the subjects had partial success while another 29 percent had complete success with the drug.[133] The study measured success in terms of the patients' ability to abstain from using cocaine for one to eight months.

IV. Poly-Drug-Pharmacotherapeutics

As mentioned in the first section, a large percentage of drug users in the 1980's are poly-drug users. A recent General Accounting Office report found that up to 40 percent of patients in methadone maintenance therapy for heroin abuse also abuse cocaine. Researchers expect this trend to continue into the 1990's. Of course, there will always be a need for pharmacotherapies with indications for specific drugs, but it will become increasingly useful to develop drug treatments for poly-drug users.

It appears that the vast majority of poly-drug users will abuse derivatives of cocaine and heroin. At a hearing before the Senate Judiciary Committee on August 31, 1989, witnesses testified that the drugs of the 1990's will mostly be old drugs with new distillations. For example, cocaine will continue to be popular, but as crack and bazuco, an impure cocaine paste. Similarly, heroin will continue to be popular, although as croak, the drug's smokeable form. The smokeable form of methamphetamine, called ice, is also expected to gain popularity.

This section will discuss the most promising poly-drug pharmacotherapeutic, buprenorphine. Using it in animal and human tests, researchers have studied the effectiveness of the medication in treating addictions that involve the concurrent use of heroin and cocaine.

BUPRENORPHINE

History

Almost 20 years ago, a British company, Reckitt and Coleman Products, Ltd., developed and began to manufacture buprenorphine.[134] In the United States, the American company, Norwich Eaton Pharmaceuticals, Inc., now distributes the drug under the trade name Buprenex.[135] The FDA has approved it as a treatment

---

[132] Warnings and adverse effects in *Ibid.*, p. 143.

[133] "Consideration of Personality Factors in Psycholpathology," *Bilogical Psychiatry*, 25:10A-13A, 1989, p. 13A.

[134] J.H., "Lukewarm Turkey," *Scientific American*, March 1989, p. 32.

[135] Edward R. Barnhart, *Physicians' Desk Reference* (Oradell, N.J.: 1989), p. 1478.

for acute and chronic pain. As an opiate treatment agent, buprenorphine is in phase II-type testing; and as a cocaine treatment, it is in the clinical evaluation stage of development.[136]

Pharmacology

With regard to treating heroin addiction, buprenorphine is an agonist-antagonist.[137] It acts as an analgesic by binding to opiate receptors in the central nervous system.[138]

However, buprenorphine's effects vary with its dosage. It acts as an opiate agonist when small doses are applied, and as an opiate antagonist when larger doses are administered.

Its slow rate of disassociation from opiate receptors accounts for its long-acting nature.[139] Like methadone, one dose will prevent narcotics withdrawal symptoms for 24 hours.

As a treatment for cocaine buprenorphine may block the euphoric effects of the illicit drug. It is unclear exactly how buprenorphine works in this capacity.

Adverse Effects

The manufacturer warns that there have not been adequate tests performed with the drug on pregnant women.[140] Minor adverse effects are common. For instance, 66 percent of those taking buprenorphine experience sedation, and 5–10 percent of them complain of nausea and dizziness.[141]

Effectiveness

A recent study conducted by Dr. Nancy Mello found buprenorphine effective at suppressing cocaine craving among rhesus monkeys. The study, reported in the August 25, 1989, edition of *Science,* described two interrelated findings.

First, proper administrations of buprenorphine to the monkeys over a 30-day period resulted in an approximately 96-percent reduction in the number of times they self-injected cocaine.

And, second, under the same conditions, the treatment yielded an approximately 94-percent reduction in the amount of cocaine they injected.[142]

That researchers obtained these results in monkeys is particularly encouraging; monkeys are excellent predictors of human responses. In fact, NIDA uses them for testing the human potential of investigational drugs.

Another study, conducted by Dr. Thomas Kosten, found that buprenorphine works well as a poly-drug treatment in human subjects. The comparative study is published in the June 5, 1989, edition of *Life Sciences.*[143] It reports that "substantially less cocaine

---

[136] *NIDA Notes,* vol. 4, No. 1, Winter 1988/1989, p. 5.
[137] Information obtained from NIDA's legislative affairs department.
[138] Edward R. Barnhart, *Physicians' Desk Reference* (Oradell, N.J.: 1989), p. 1476.
[139] *Ibid.,* p. 1477.
[140] Edward R. Barnhart, *Physicians' Desk Reference* (Oradell, N.J.: 1989), p. 1477.
[141] *Ibid.,* p. 1477.
[142] Nancy Mello, "Buprenorphine Suppresses Cocaine Self-Administration by Rhesus Monkeys," *Science,* Aug. 25, 1989, p. 860.
[143] Thomas R. Kosten, "Role of Opioid Antagonists in Treating Intravenous Cocaine Abuse," *Life Sciences,* vol. 44, No. 13, 1989, 887–892.

abuse was detected during either naltrexone or buprenorphine treatment than during initial methadone treatment." [144]

Issues

The Mello study hypothesizes an interrelation between the opioid and dopaminergic systems in the brain.[145] Specifically, the hypothesis maintains that the dopaminergic system modulates endogenous opioid system activity, and that the converse is true as well.

This discovery holds profound implications for pharmacotherapy. If the two systems interact, there is a strong chance that particular drugs might simultaneously treat dual narcotics and cocaine addictions. In other words, if the hypothesis proves true, there is reasonable hope that researchers will discover more treatments for polydrug use.

The Kosten study hypothesizes that narcotic antagonists probably do not directly block cocaine effects. Instead, the study proposes, they act indirectly to reduce drug use by "depriving the user of an agent to reduce cocaine induced 'crash' dysphoria." [146] In other words, if drug users take narcotic antagonists, they will not be able to ease their post-cocaine depression with narcotics because the medications will block any narcotic action. In the absence of relief mechanisms (narcotics), there would be little enticement for users to continue using cocaine.

Because buprenorphine has certain opioid properties, it is possible for patients to acquire a psychological dependence to it. Little physical dependence occurs, however, the withdrawal from it is less severe than with heroin and shorter than with methadone.[147] As the withdrawal syndrome is relatively minor, patients who are comfortable with their acquired ability to refuse narcotics and cocaine may cease their maintenance treatment and become completely detoxified. The less severe withdrawal symptoms and the possibility of using buprenorphine as a maintenance drug make it an attractive alternative for methadone.

- Buprenorphine offers two more improvements over methadone.
  - —First, buprenorphine has a lower chance of spawning an illicit market.[148] Although the drug has opioid properties, they are not as prevalent as those of methadone. This is especially the case given buprenorphine's antagonist qualities. Because the narcotic action is relatively weak, street users will receive little satisfaction from abusing the drug.
  - —And, second, there is not as great a chance of overdose with buprenorphine as with methadone. Buprenorphine has an antagonist opioid component to prevent lethal overdose, "even at ten times the analgesic therapeutic dose." [149]

---

[144] *Ibid.*, p. 890.
[145] Nancy Mello, "Buprenorphine Suppresses Cocaine Self-Administration by Rhesus Monkeys," *Science*, Aug. 25, 1989, p. 861.
[146] Thomas R. Kosten, "Role of Opioid Antagonists in Treating Intravenous Cocaine Abuse," *Life Sciences*, vol. 44, No. 13, p. 890.
[147] J.H., "Lukewarm Turkey," *Scientific American*, March 1989, p. 32.
[148] Nancy Mello, "Buprenorphine Suppresses Cocaine Self-Administration by Rhesus Monkeys," *Science*, Aug. 25, 1989, p. 860.
[149] *Ibid.*, p. 860.

V. Recommendations: A Strategy for the 1990's

There are at least 30 pharmacotherapeutics for illicit drug use currently under investigation.[150] That so many medications are now being studied proves that the system is not stagnant. Yet it is not vibrant, either. Broad and decisive action must be taken now if the United States is to have any hope of realizing the numerous benefits of pharmacotherapy.[151]

America needs a National Strategy to develop pharmacotherapeutics. Unfortunately, the President's National Drug Strategy does not provide a comprehensive plan for the development of such medications.

As a consequence, this report concludes with a proposed National Pharmacotherapy Strategy, a plan to enhance the development and/or promotion of the eight medications discussed above, and others, over the course of the next 10 years.

As in the first section of this report, the term "pharmacotherapeutics" refers to medications used to help recovering addicts.

GOALS FOR A PHARMACOTHERAPY STRATEGY

Goals are the foundation of a strategy. A strategy must define what is necessary before outlining the means to achieve it. The President Strategy lacks any goals for pharmacotherapeutic development. The Strategy mentions treatment drugs and notes that they may be useful, but it does not establish priorities or provide a timetable for developing them.

Goals are also a means of measuring the success of any plan. Strategies are successful once they have reached their milestones. If there are no milestones, it is difficult to determine how much ground, if any, has been covered. America needs to be certain that it is making headway in the field of drug treatment. Because the President's Strategy is vague with regard to pharmaco-therapy, America cannot be sure that, under it, adequate progress will be made.

To meet America's need for specific and reasonable milestones, this report offers the following 10 goals for pharmacotherapeutic research and development:

1. Launch and fully staff a large-scale program for the development of drug treatments within one year.

The first step is to create and staff a program that will be capable of directing the research and development of pharmacotherapeutic. Under the program's direction, the remaining goals will be accomplished.

2. Implement new FDA guidelines for the safety and efficacy trials of pharmacotherapeutics within 1 year.

With guidelines that define the Government's expectations of pharmacotherapeutics, manufacturers can develop medications more efficiently and the FDA can hasten its scrutiny of those medications.

---

[150] Some of them are old drugs for which researchers are seeking new indications, and others are entirely new treatments without any FDA approval.

[151] As mentioned above, by law, pharmacotherapy clinics must provide counselling to those who receive drug treatment. This report recommends that this law be maintained for the foreseeable future.

3. Make available a methadone alternative within 3 years.

Methadone has been very effective, but it is not a panacea for narcotics addiction. Patients need an alternatives to methadone that will increase the chances of their recovery. LAAM might satisfy this goal.

4. Develop new, secure methods of treating drug addicts within 3 years.

Current treatment methods, especially with narcotics agonists, encounter such security programs as spawning illicit markets. Pharmacotherapy clinics must be able to help addicts without inadvertently generating a broader drug problem.

5. Make available a long acting narcotic antagonist within 3 years.

One problem with the present antagonists naltrexone aned naloxone is that a physician must administer them at short intervals. These repeated administrations increase the likelihood that patients will miss, or decide to forego, further treatment. With a longer acting antagonist, patients can capitalize on their initial desire to recover. A depot form of naltrexone might satisfy this goal.

6. Make available a poly-drug treatment within 4 years.

As noted above, drug users of the 1990's will likely continue the current trend of poly-drug use. Accordingly, a poly-drug medication is necessary to meet this new treatment challenge. Buprenorphine might satisfy this goal.

7. Develop a cocaine-blocking treatment within 4 years—and make it available within 7 years.

Like a narcotic antagonist for stimulants, a cocaine blocker will prevent addicts from feeling any pleasure as a result of cocaine use. This "cocaine antagonist" will provide patients with a means to extinguish their habits.

8. Develop and make available a methamphetamine treatment within 6 years.

Methamphetamine and its smokeable form "ice" are becoming increasingly popular drugs. To help the growing number of people addicted to methamphetamine, researchers should develop medications for it.

9. Develop a cocaine-blocker/narcotics antagonist drug within 6 years—and make it available within 9 years.

Used alone or in conjunction with another poly-drug medication such a buprenorphine, this medication will allow heroin/cocaine users to extinguish their addictions.

10. Provide effective pharmacotherapeutic treatment on demand for cocaine and heroin addicts within 10 years.

For America to win its war against drugs, users must be able to receive treatment on demand. And pharmacotherapeutic treatment on demand for heroin and cocaine users by the year 2000 is a realistic goal.

THE STRATEGY IN OUTLINE

To achieve these ambitious goals, America must undertake a great initiative. Accordingly, this report recommends a five-part

plan to accelerate the research, development, and production of pharmacotherapeutics. The five parts in broad outline are:

1. Launching a renewed "Medications Development Program."
2. Modifying the Orphan Drug Act to add incentives for the development of pharmacotherapeutics.
3. Hastening the use of new drug treatments.
4. Designating certain areas of research "Top Priorities" at the new Medications Development Program.
5. Producing a Surgeon General's report on pharmacotherapy.

Each of these recommendations is discussed in detail below.

1. Launch a renewed "Medications Development Program"

Our first priority must be a lauch a large-scale, national "Medications Development Program" that will vastly accelerate the research and development of new pharmacotherapies. Congress should devote approximately $1 billion over 10 years to this effort.

The Anti-Drug Abuse Act of 1988 authorized $10 million for NIDA to establish a program that would develop treatment drugs. With the funding, NIDA created the Medications Development Program (MDP). The MDP is a consortium effort meodeled after the National Cancer Institute. Accordingly, it coordinates the research and testing efforts of the Government, private industry, and academic community to promote the development of pharmacotherapeutics.

The MDP acts as a liaison between private industry and the academic community. Based on government and university research, the MDP approaches pharmaceutical companies and suggests that certain of their drugs may be useful for drug treatment.[152] If the companies consent, the MDP conducts low-level tests on the drugs. Once the medications complete this first phase, the MDP contracts out for other testing. At the conclusion of these tests, the MDP turns the drugs over to any of seven university-based testing centers. There, the drugs undergo clinical tests and continue to fulfill IND requirements.

The MDP's liaison function is important because most of the drugs that the program tests are old ones owned by private companies. Yet the MDP also seeks to develop new and previously unapproved compounds. To that end, the MDP may sponsor medications pioneered by NIDA scientists and academic researchers; the drugs under development need not come from private industry.

The MDP is a fledgling effort. Still, its emerging system for developing drug treatments appears to be essentially well designed.

To take full advantage of this evolving system, it is necessary to promote the MDP initiative on a much more substantial level.

Thus, this report recommends that the Medications Development Program be renewed, codified, and made permanent. Specifically, Congress should create an official MDP and give the MDP its own, independent funding. Today's MDP should be re-

[152] Of course, pharmaceutical companies may spontaneously submit their drugs to the MDP for consideration. NIDA could determine and/or limit the current MDP.

placed by this enhanced entity which could not be abolished or curtailed by NIDA.[153]

This report further recommends that the MDP be a hub for pharmacotherapeutic development into the 21st century. To achieve this goal, Congress should fund the MDP at approximately $1 billion over the next decade. The total funding level would be divided according to the following schedule:

Fiscal Year 1991 $60 million
Fiscal Year 1992 $70 million
Fiscal Year 1993 $75 million
Fiscal Year 1994 $85 million
Fiscal Year 1995 $90 million
Fiscal Year 1996 $100 million
Fiscal Year 1997 $110 million
Fiscal Year 1998 $120 million
Fiscal Year 1999 $135 million
Fiscal Year 2000 $150 million

With the assured, increased funding level, the MDP would shift from its current status as a "branch" to become a "division" within NIDA.

How would the renewed MDP look?

- Congress would add a Director, who would be aided by two Deputy Directors.
- The MDP's staff would grow from its current level of five full-time professionals to at least 50 clinical field researchers.

The new MDP Director would be required to submit within 6 months a report to the Office of National Drug Control Policy detailing the program's objectives and goals. This report should be incorporated into the ONDCP's National Strategy Report.

The MDP should complete negotiations with the FDA that would establish guidelines for the safety and efficacy trials of pharmacotherapeutics. These guidelines would apply to phase II and III testing. The absence of guidelines designed explicitly for pharmacotherapeutics has hampered the development and approval of treatment medications. The MDP should conduct monthly meetings with the FDA to discuss other measures that may facilitate the approval process for drug treatments.

The program is ambitious and, on a expanded basis, will benefit pharamacotherapy greatly. The benefits include:

- A broader research base.
- An increased volume of drug treatment research.
- An increased chance of discovering new treatments.
- An increased number of IND sponsorships for drug treatments.
- An accelerated development of pharmacotherapeutics.
- A hastened process for FDA drug treatment approval.
- An augmented respect for drug treatment research.

The basic intent of this report is to further the research, development and production of pharmacotherapeutics. A renewed MDP—with its funding levels boosted to $100 million per year—is the main vehicle by which this report hopes to carry out its intentions.

---

[153] The Orphan Drug Act defines "rare diseases" as those afflicting fewer than 200,000 people.

In sum, Congress should enact legislation creating a renewed MDP, fully fund this program, and elevate its status in our national "war on drugs."

2. Modify the Orphan Drug Act

For the reasons presented in the first section of this report, private industry has not taken a major, leading role in pharmacotherapeutic investigation and development. In response to this problem, the government should take two steps:

A. Extend the Orphan Drug Act's protection to include pharmacotherapeutics

Enacted in 1983, the Orphan Drug Act offers exclusive marketing arrangements to companies that develop drugs to treat rare diseases.[154] The act provides pharmaceutical companies with the incentive to research, develop, and produce necessary, but otherwise unprofitable, drugs such as the small pox vaccine.

The FDA has granted "orphan drug" status to certain medications used in treating heroin addiction. However, it is less likely that, under current guidelines, this status will be granted for medications used in treating cocaine addictions as there are significantly more people addicted to cocaine than to heroin. Still, as noted above, this larger population does not necessarily translate into a profitable base for distribution. Thus, the act's protective scope must be expanded to include these treatment drugs.

Dr. Charles Schuster of the National Institute on Drug and Alcohol Abuse recently testified before the Senate Judiciary Committee that—

> Even though the addictive disorders do not meet the technical criteria of orphan drug restrictions, the lack of private sector effort in developing medications to treat additions suggests that they have become in effect orphan conditions.

In an amendment to S. 1711, adopted by the Senate on October 5, 1989, Senators Joseph R. Biden, Jr., and Edward M. Kennedy proposed extending protection under the Orphan Drug Act to include pharmacotherapeutics. Congress should enact this proposal into law as quickly as possible.

B. Stiffen the act's enforcement mechanisms

The Orphan Drug Act provides patent-like protection to certain drugs that have never before been patented. Yet it does not protect the manufacturing rights of companies whose drug patents have expired prior to their discovering new indications, or uses, for those drugs.

To illustrate this point, consider the following example: Once a company produces a drug X under patent and that patent expires, other companies may produce drug X generically. If the original manufacturer discovers and patents a new use for X after the drug's original patent has expired, other firms may continue to

---

[154] Dr. Charles Schuster, prepared statement for an Aug. 31, 1989, hearing titled "Drugs in the 1990's: New Perils, New Promise," p. 4.

produce drug X, albeit not for the new use. In reality, though, physicians and clinics may prescribe the generic drug for the new use despite the new patent. They understand that the generic brand of X is the same as X, and, therefore, an effective treatment even for the new use. The act does nothing to protect the profits of manufacturers who fall prey to this enforcement loophole. Therefore, the act should be strengthened accordingly.

This problem will apply particularly to the older medications now being studied for cocaine treatment. Their patents have expired, or soon will, and private companies need assurance that it will be profitable to seek new indications for them.

Congress should enact modifications to the Orphan Drug Act to encourage the development of new uses for old drugs.

3. Hasten the use of new drug treatments

A broad problem presented above is the difficulty pharmaceutical companies have in receiving FDA approval for their drugs. In one sense, the slow process is a safe one, but, in another sense, it is dangerous. There is safety in long deliberation over the effectiveness and harms of a drug. However, there is danger in certain drugs never, or only slowly, reaching market. In other words, the FDA would rather err with mistakes of omission than with mistakes of commission. This mind-set has resulted in the FDA's using an approval system that is often slower than safety would require.

The FDA has instituted two innovative procedures to speed the research and distribution of AIDS treatments. This report recommends that the FDA adapt these procedures to pharmacotherapy for illicit drug use as well.

A. Institute "Treatment Investigational New Drugs"

First, there is the concept of the Treatment Investigational New Drug. This idea provides for treatment patients with certain medications that have not yet received final FDA approval. It has been effectively used in the AIDS arena, and the approach should be applied to pharmacotherapy.

If this initiative is successful, recovering addicts will have access to medications perhaps years before the drugs would otherwise have reached market.

B. Institute "Parallel Track Trials"

The second innovative measure the FDA undertook to handle the AIDS epidemic was to allow parallel track trials. Under this provisions, researchers have access to drugs that Government studies have proven safe but that have not yet completed the FDA's efficacy testing.

The FDA monitors the results realized by the doctors using parallel track drugs and employs that information to complete the Phase III requirements.

Since the FDA will already have deemed many of the pharmacotherapeutics safe for other indications, it is unlikely that they will cause harm. More likely, they will effectively combat drug abuse. This proposal, similar to the one for treatment investigational new drugs, may make important pharmacotherapeutics available for use long before the current system would have allowed.

C. Forego "Mechanism of Action" Requirement for Previously Approved Pharmacotherapeutics

In the 1970's, the FDA mandated that a drug's "mechanism of action" must be known for it to receive the Administration's approval. This requirement prevents the approval of "dirty drugs," or medications that have effective yet unknown pharmacological action in the human body.

Many of the drugs currently under investigation for cocaine treatment are ones that received their original approval prior to the FDA's instituting the "mechanism of action" requirement. Some of the pharmacotherapeutics mentioned in this report—such as carbamazepine, desipramine, and imipramine—are "dirty drugs." Despite the negative label, the drugs are effective and safe, as years of their use have proven.

Under the current FDA system, even drugs that were approved prior to the 1970's regulation must provide their "mechanism of action" for any new indications.

The extra requirement slows the approval process for drug medications. More importantly, the requirement is superfluous given the known practical histories of previously approved drugs. From the histories, physicians can predict the drugs' adverse effects and pharmacological consequences. The drugs have not changed, only the theories surrounding their administration. Therefore, there is no need to waylay such previously approved pharmacotherapeutic candidates with the "mechanism of action" regulation.

Congress should enact legislation that repeals the "mechanism of action" requirement for pharmacotherapeutics.

D. Legislate a "Rolling IND" Concept for Pharmacotherapeutics

The FDA must approve a drug for the IND stage of development. Normally, a pharmaceutical company submits an IND application as a whole to the FDA, which then has 30 days to approve or disapprove that application. If any portion of the application does not meet FDA standards or protocol, the Administration may reject the entire application. In such cases, the company must completely resubmit an application on the rejected drug's behalf at a later date. This system makes the IND approval process much more difficult than necessary, and, thus, slows the development of treatment drugs.

The "rolling IND" concept would allow a company applying for a pharmacotherapeutic IND to submit information about the drug to the FDA as that information comes available. The difference in the processes, then, is that "rolling IND" applications do not have to be submitted as a completed whole. Rather, a company may submit them in parts.

With the "rolling IND," the FDA can inform a company of its application's problems as they arise. A company can subsequently resubmit the unapproved parts of the application while compiling the remainder of the it. By the time the last part of the application is submitted, the company would have, in theory, resubmitted previously rejected parts and received approval on them. This "rolling" process provides the quickest, surest possible means for a com-

pany to receive the FDA's approval for the IND applicant. And the faster the drug meets this initial approval, the sooner it can complete its IND testing requirements.

4. Designate the following areas of research "top priorities" at the renewed MDP

This report finds that several facets of pharmacotherapy, despite their great importance, have not received adequate investigation. Accordingly, the MDP should assign to them "top priority" status.

A. The Effects of Pharmacotherapeutics on Pregnant Women and Their Fetuses

Since the popular rise of crack cocaine, women have increasingly become the victims of drug abuse. It is a grave concern that women, if pregnant, endanger not only their own lives but also the lives of their unborn children. All drug abuse needs to cease, but among pregnant women, this need has a special urgency. In light of the problem, researchers should investigate, as part of the drug testing process, the effects that pharmacotherapeutics have on pregnant women and their unborn children.

Researchers should also investigate the levels of potential drug treatments found in the milk of nursing mothers.

Pregnant women must be made to feel secure in the safety of the medications they take. If they feel safe, they will more likely seek treatment for their drug addictions. And, in doing so, they will save themselves as well as their unborn children.

B. Treatment for "New" Drugs of the 1990s

Researchers have not produced pharmacotherapeutics that address specifically the "new" drugs that may become popular in the 1990's. As mentioned above, methadone alone will not suffice as a treatment for addicts who abuse various "designer" drugs and/or cocaine distillations.

The MDP should study the pharmacology of methamphetamine and propose possible drug medications. Depending on the results of the MDP's study, cocaine pharmacotherapeutics should be tested for their viability as methamphetamine treatments.

C. The Proposed Interaction Between Heroin and Cocaine Pharmacologic Mechanisms

Recent evidence that dopaminergic and opioid systems may be interdependent should prompt further investigation.

Exploiting this hypothesized interdependence may prove the key to treating the poly-drug users of today and tomorrow. NIDA, recognizing the importance of confirming the hypothesis, has expressed interest in pursuing research on buprenorphine.

Research should be conducted concerning the viability of using cocaine-specific and heroin-specific treatment simultaneously. If such treatments prove safe, poly-drug users could be treated irrespective of the veracity of the interdependence hypothesis.

5. Produce a surgeon general's report on pharmacotherapy

A Surgeon General's report on pharmacotherapy, similar to Dr. Koop's AIDS Report, should be produced by March 1, 1991. To ac-

complish this task, the renewed MDP should convene a "blue ribbon" panel that will assess the national drug strategy for pharmacotherapy and make appropriate recommendations. The report would provide Americans with the scientific repercussions of drug abuse, and would further provide them with comprehensive information on pharmacotherapy and the means of receiving it. Such a factual, level-headed approach to explaining the consequences of illicit drug use may convince many of the real dangers involved.

○